IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, v. HOSPIRA, INC. and PFIZER INC., Defendants.	C.A. No. 18-1064-CFC DEMAND FOR JURY TRIAL

FIRST AMENDED AND SUPPLEMENTAL COMPLAINT

Plaintiffs Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Plaintiffs"), by and through their undersigned attorneys, for their First Amended and Supplemental Complaint against Defendants Hospira, Inc. and Pfizer Inc. (collectively, "Defendants") hereby allege as follows:

THE PARTIES

1. Amgen Inc. is a corporation existing under the laws of the State of Delaware, with its principal place of business at One Amgen Center Drive, Thousand Oaks, California, 91320. Amgen Inc. discovers, develops, manufactures, and sells innovative therapeutic products based on advances in molecular biology, recombinant DNA technology, and chemistry. Founded in 1980, Amgen Inc. is a pioneer in the development of biological human therapeutics. Today, Amgen Inc. is one of the largest biotechnology companies in the world, fueled in part by the success of NEUPOGEN® (filgrastim).

2. Amgen Manufacturing, Limited ("AML") is a corporation existing under the laws of Bermuda with its principal place of business in Juncos, Puerto Rico. AML manufactures and

sells biologic medicines for treating particular diseases in humans. AML is a wholly-owned subsidiary of Amgen Inc.

3. On information and belief, Hospira, Inc. ("Hospira") is a corporation existing under the laws of the State of Delaware, with its principal place of business at 275 North Field Drive, Lake Forest, Illinois 60045.

4. On information and belief, Pfizer Inc. ("Pfizer") is a corporation existing under the laws of the State of Delaware, with its principal place of business at 235 East 42nd Street, New York, New York 10017.

5. On information and belief, Hospira is a wholly-owned subsidiary of Pfizer.

6. On information and belief, Defendants collaborate to develop, manufacture, seek regulatory approval for, import, market, distribute, and sell biopharmaceutical products (including products intended to be sold as biosimilar versions of successful biopharmaceutical products developed by others) in this judicial District and throughout the United States.

NATURE OF THE ACTION

7. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, including 35 U.S.C. § 271(e)(2)(C), which was enacted in 2010 as part of the Biologics Price Competition and Innovation Act ("the BPCIA").

8. By amendment to the Public Health Service Act, the BPCIA created a new, abbreviated pathway for the approval of biological products that are highly similar to previously-licensed innovative biological products. Codified at 42 U.S.C. § 262(k), the new abbreviated pathway, often referred to as "the subsection (k) pathway," allows a biosimilar applicant to secure a license from the Food and Drug Administration ("the FDA") by relying on a prior license granted to an innovator company ("the Reference Product Sponsor" or "RPS") for its innovative biological product ("the reference product"). The reference product must have been

licensed by the FDA under the innovator pathway of 42 U.S.C. § 262(a), often referred to as "the subsection (a) pathway," which requires proof of safety and efficacy through a series of phased clinical trials.

9. In this case, Hospira is a biosimilar applicant acting in concert with Pfizer, its corporate parent, and Amgen Inc. is a Reference Product Sponsor. Hospira sought FDA licensure under the subsection (k) pathway for a biosimilar version of Amgen Inc.'s NEUPOGEN® (filgrastim) product.

10. Seeking the benefits of the subsection (k) pathway, Hospira, acting in concert with Pfizer, submitted its abbreviated Biologic License Application ("aBLA") No. 761080 ("the Hospira aBLA") to the FDA, requesting that its biological product ("the Hospira Filgrastim Biosimilar Product") be licensed by relying on Amgen Inc.'s demonstration of the safety and efficacy of NEUPOGEN® (filgrastim).

11. The asserted patent is U.S. Patent No. 9,643,997 ("the '997 Patent"), attached hereto as Exhibit 1. The '997 Patent is directed to methods of purifying proteins used in the manufacture of a biological product.

12. On information and belief, Hospira, acting in concert with Pfizer, submitted the Hospira aBLA to the FDA before the expiration of the '997 Patent.

13. Amgen Inc. included the '997 Patent on its February 8, 2018 disclosure under 42 U.S.C. § 262(*l*)(3)(A).

14. Here, Defendants committed an act of infringement as to the '997 Patent under 35 U.S.C. § 271(e)(2)(C) when they caused Hospira to submit the Hospira aBLA, including on information and belief, any amendments thereto, for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, or sale of the Hospira Filgrastim Biosimilar Product.

15. On July 20, 2018, Hospira and Pfizer received FDA approval for NIVESTYM™ (filgrastim-aafi). Pfizer's news release dated July 20, 2018, attached hereto as Exhibit 2, states: "Pfizer Inc. (NYSE:PFE) today announced that the United States (U.S.) Food and Drug Administration (FDA) has approved NIVESTYM™ (filgrastim-aafi), a biosimilar to Neupogen (filgrastim), for all eligible indications of the reference product." Pfizer's 10-Q dated November 8, 2018 and filed with the U.S. Securities and Exchange Commission, attached hereto as Exhibit 3, states: "Product: Nivestym (filgrastim-aafi); Indication: A biosimilar to Neupogen® (filgrastim) for all eligible indications of the reference product; Date Approved: July 2018." Exhibit 3, Pfizer's Form 10-Q, at 82.

16. At least by September 24, 2018, Defendants began to import the Hospira Filgrastim Biosimilar Product into the United States, and Defendants began to offer to sell, sell, or use the Hospira Filgrastim Biosimilar Product within the United States. For example, FDA's National Drug Code Directory lists a Nivestym™ "Start Marketing Date" of September 24, 2018. *See* Exhibit 4, FDA, NAT'L DRUG CODE DIRECTORY SEARCH RESULTS FOR "NIVESTYM" (Mar. 20, 2019), https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm.

17. By Defendants' importation of the Hospira Filgrastim Biosimilar Product into the United States, or offer to sell, sale, or use of that product within the United States, Defendants have infringed and/or will infringe Claims 17, 18, and 26 of the '997 Patent, literally or equivalently, under 35 U.S.C. § 271(g).

JURISDICTION AND VENUE

18. This action arises under the patent laws of the United States, Title 35 of the United States Code, Title 42 of the United States Code, and under the Declaratory Judgment Act of 1934 (28 U.S.C. §§ 2201-2202), Title 28 of the United States Code. This Court has subject-matter jurisdiction under 28 U.S.C. §§ 1331, 1338(a), 2201(a), and 2202.

19. This Court has personal jurisdiction over Hospira because, among other things, on information and belief, Hospira is a Delaware corporation, has conducted business in this District, has availed itself of the rights and benefits of Delaware law, and has engaged in substantial and continuing contacts with Delaware.

20. This Court has personal jurisdiction over Pfizer because, among other things, on information and belief, Pfizer is a Delaware corporation, has conducted business in this District, has availed itself of the rights and benefits of Delaware law, and has engaged in substantial and continuing contacts with Delaware.

21. Amgen Inc. is a Delaware corporation and has suffered injury in Delaware as a result of the Defendants' infringement of Amgen Inc.'s patent.

22. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b) and (c), and 28 U.S.C. § 1400(b) at least because, on information and belief, each Defendant is a corporation incorporated in the State of Delaware.

BACKGROUND

A. Amgen Inc.'s innovative biological product, NEUPOGEN® (filgrastim)

23. The active ingredient in Amgen Inc.'s NEUPOGEN® (filgrastim) is filgrastim, a recombinantly expressed, 175-amino-acid form of a protein known as human granulocyte-colony stimulating factor ("G-CSF"). NEUPOGEN® (filgrastim) is indicated to (1) decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs; (2) reduce the time to neutrophil recovery and duration of fever, following induction or consolidation chemotherapy treatment of adults with Acute Myeloid Leukemia (AML); (3) reduce the duration of neutropenia and neutropenia-related clinical sequelae in cancer patients undergoing bone marrow transplantation; (4) mobilize autologous hematopoietic progenitor cells into the peripheral blood

for collection by leukapheresis; (5) reduce the incidence and duration of sequelae of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, and idiopathic neutropenia; and (6) increase survival in patients acutely exposed to myelosuppressive doses of radiation.

24. By binding to specific receptors on the surface of certain types of cells, NEUPOGEN® (filgrastim) stimulates the production of a type of white blood cell known as neutrophils. Neutrophils are the most abundant type of white blood cells and form a vital part of the human immune system. A deficiency in neutrophils is known as neutropenia, a condition which makes the individual highly susceptible to infection. Neutropenia can result from a number of causes; it is a common side effect of chemotherapeutic drugs used to treat certain forms of cancer. NEUPOGEN® (filgrastim) counteracts neutropenia.

25. The availability of NEUPOGEN® (filgrastim) represented a major advance in cancer treatment by protecting chemotherapy patients from the harmful effects of neutropenia and by thus facilitating more effective chemotherapy regimens.

26. Amgen Inc. is the sponsor of the BLA for NEUPOGEN® (filgrastim).

27. AML is a wholly-owned subsidiary of Amgen Inc. AML manufactures NEUPOGEN® (filgrastim).

28. Amgen USA Inc. is a wholly-owned subsidiary of Amgen Inc. Amgen USA Inc. purchases NEUPOGEN® (filgrastim) from AML, and is the distributor of NEUPOGEN® (filgrastim) in the United States.

29. Plaintiffs profit from each sale of NEUPOGEN® (filgrastim) in the United States.

B. Defendants sought approval to market a biosimilar version of NEUPOGEN® (filgrastim) by taking advantage of the abbreviated subsection (k) pathway of the BPCIA

30. Defendants sought approval from the FDA to sell a "biosimilar" version of NEUPOGEN® (filgrastim) by taking advantage of a new, abbreviated approval pathway under the BPCIA.

31. Congress enacted the BPCIA on March 23, 2010. The purpose of the BPCIA is to establish "a biosimilars pathway balancing innovation and consumer interests." Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, § 7001(b), 124 Stat. 119, 804 (2010) (amending 42 U.S.C. § 262). The statutory requirements of the BPCIA reflect Congress's intent to achieve this balance.

32. The BPCIA created the subsection (k) pathway, 42 U.S.C. § 262(k), for FDA licensure of biological products upon a determination that the biological product is "biosimilar" to a previously-licensed "reference product." The BPCIA defines a "biosimilar" to be a biological product that: (1) is "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and (2) has "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." 42 U.S.C. §§ 262(i)(2)(A) and (B). The BPCIA defines a "reference product" to be "a single biological product licensed under subsection (a) against which the biological product is evaluated in an application submitted under subsection (k)." 42 U.S.C. § 262(i)(4).

33. As opposed to applicants following the § 262(a) pathway, biosimilar applicants following the § 262(k) pathway have the advantage of referencing the innovator's license—the FDA evaluates the safety and efficacy of the applicant's biological product by relying on the innovator's prior demonstration of safety, purity, and potency of the reference product.

Specifically, the § 262(k) pathway may only be used where the prior applicant for the reference product has submitted an application under 42 U.S.C. § 262(a) for approval of a reference product, and the FDA has determined that the Reference Product Sponsor has demonstrated that "the biological product that is the subject of the application is safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I).

34. Before the BPCIA, reference to another's biological license could be made only with the permission of the Reference Product Sponsor. An innovator RPS enjoyed permanent and exclusive rights to its clinical trial data and FDA license. The BPCIA advanced the public's interest in price competition in part by diminishing these rights, allowing a biosimilar applicant to "reference" the innovator RPS's license rather than incurring the delay and costs of generating its own clinical data.

35. Consequently, the subsection (k) pathway allows the biosimilar applicant to avoid the time and expense incurred by the RPS for development and clinical testing, and to gain licensure to commercialize its biological product in the market sooner as a biosimilar than it could have done through an independent demonstration of safety, purity, and potency under the § 262(a) pathway. The subsection (k) pathway is thus referred to as an "abbreviated" approval pathway.

36. In addition to providing these benefits, approval under the subsection (k) pathway offers another benefit to the biosimilar applicant: a product that is approved as a biosimilar can take advantage of the existing market for the reference product created by the RPS.

37. On information and belief, Hospira, acting in concert with Pfizer, submitted the Hospira aBLA to the FDA under the subsection (k) pathway. The Hospira aBLA sought approval to commercially manufacture, use, offer to sell, sell, and import into the United States, the

Hospira Filgrastim Biosimilar Product, a biosimilar version of Plaintiffs' NEUPOGEN® (filgrastim) product.

38. The applicant named in the Hospira aBLA is "Hospira, Inc., a Pfizer Company." The Hospira Filgrastim Biosimilar Product is described in the Hospira aBLA as PF-06881893.

39. The Hospira Filgrastim Biosimilar Product is designed to copy and compete with Amgen Inc.'s NEUPOGEN® (filgrastim). Hospira has and/or will instruct or direct others to administer the Hospira Filgrastim Biosimilar Product to certain patients in the U.S. to treat particular diseases in the same way that Amgen Inc.'s NEUPOGEN® (filgrastim) is administered. Hospira sought FDA approval for one or more indications for which NEUPOGEN® (filgrastim) is already approved.

40. Amgen Inc. holds Biologic License Application ("BLA") No. 103353 for filgrastim and is therefore the Reference Product Sponsor with respect to any biosimilar versions of filgrastim. Hospira did not seek to independently demonstrate to the FDA that its biological product is "safe, pure, and potent" pursuant to 42 U.S.C. § 262(a), as Amgen Inc. did in its BLA for its innovative biological product NEUPOGEN® (filgrastim). Rather, Hospira requested that the FDA evaluate the suitability of its biological product for licensure by expressly referencing NEUPOGEN® (filgrastim) and thereby relying on the data supporting Amgen Inc.'s FDA license for NEUPOGEN® (filgrastim). 42 U.S.C. § 262(k)(2)(A)(iii)(I).

C. The information exchange under 42 U.S.C. § 262(*l*)

41. In addition to creating an abbreviated pathway for the approval of biosimilars, the BPCIA also creates an intricate and carefully orchestrated set of procedures for the biosimilar applicant and the RPS to engage in a series of information exchanges and good-faith negotiations between parties prior to the filing of a patent infringement lawsuit. These exchanges are set forth

in 42 U.S.C. §§ 262(*l*)(2) through (*l*)(5) and culminate in an "immediate patent infringement action" pursuant to 42 U.S.C. § 262(*l*)(6).

42. On December 4, 2017, Defendants, through their counsel, sent a letter to Amgen Inc. providing notice that the Hospira aBLA "was recently accepted for filing by FDA" and that "Pfizer intends to provide [Amgen Inc.], as the holder of BLA No. 103353 for filgrastim and the 'reference product sponsor,' a copy of the [Hospira aBLA]." Through its counsel, Amgen responded on December 8, 2017, designating outside counsel and in-house counsel to have access to the Hospira aBLA.

43. Under 42 U.S.C. § 262(*l*)(2)(A), Defendants were required to provide to Amgen Inc. "a copy of the application submitted to [the FDA] under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application."

44. On December 11, 2017, Defendants produced some sections of the Hospira aBLA to Amgen Inc. with a cover letter indicating that Defendants were providing "the full" Hospira aBLA.

45. Following a brief review of Defendants' December 11 production, counsel for Amgen Inc. suspected that Defendants had not produced their entire aBLA, and on December 12, 2017, counsel for Amgen Inc. asked Defendants' counsel to "confirm whether Pfizer has produced its entire ABLA, or whether it has redacted or withheld any portions of it." Defendants' counsel responded on December 15, 2017 indicating that Amgen Inc. "should have the entire ABLA."

46. Following further review of Defendants' production, however, it was apparent to Amgen Inc. that Defendants had not produced the entirety of the Hospira aBLA. Amgen Inc.

promptly brought this concern to Defendants' attention in a letter on December 21, 2017. In response, Defendants produced additional portions of the Hospira aBLA on December 22, 2017, and January 4, 2018, which Defendants characterized as a "few minor additional sections" of the Hospira aBLA that "were inadvertently not included with" Defendants' production on December 11, including "a couple minor items that were not included as part of module 1.1."

47. Yet, despite these repeated assurances that Defendants had produced a complete copy of the Hospira aBLA, and Defendants' supplemental productions of additional portions thereof, after continued review of Defendants' production, Amgen Inc. concluded that Defendants still had not produced numerous sections of the Hospira aBLA to Amgen Inc. In part, Amgen Inc. concluded that some sections were missing from the production because some of the missing sections were cross-referenced in the limited sections of the aBLA that Defendants had produced. Counsel for Amgen Inc. once again brought this failure to comply with § 262(*l*)(2)(A) to Defendants' attention in a letter dated January 30, 2018, which provided examples of numerous sections that were referenced in the Hospira aBLA, but had not been produced to Amgen Inc.

48. On February 13, 2018, over a week after the deadline for Amgen Inc. to serve its disclosure under § 262(*l*)(3)(A), Defendants responded to Amgen Inc.'s January 30, 2018 letter by producing additional documents that Defendants claimed "were inadvertently not included in [Defendants'] original production." This late production included over 70,000 additional pages of the Hospira aBLA, far exceeding the approximately 10,000 pages that Defendants had previously produced.

49. Despite Defendants' deficient and/or untimely disclosure under § 262(*l*)(2)(A), Amgen Inc. has nevertheless engaged in the statutory process to the extent possible. On February

8, 2018, Amgen Inc. provided its disclosure under 42 U.S.C. § 262(*l*)(3)(A) to Defendants identifying six patents that, based on the information Defendants had provided to date, Amgen Inc. believed a claim of patent infringement could reasonably be asserted if a person not licensed by Amgen Inc. engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of the Hospira aBLA (as described in the portions of the Hospira aBLA provided to Amgen Inc. on December 11 and 22, 2017, and January 4, 2018). On March 5, 2018, Amgen Inc. disclosed a newly-issued patent to Defendants under § 262(*l*)(7).

50. On April 4, 2018, Defendants provided to Amgen Inc. a statement under 42 U.S.C. § 262(*l*)(3)(B)(ii)(I), and on June 1, 2018, Amgen Inc. provided to Defendants a statement under 42 U.S.C. § 262(*l*)(3)(C).

51. Beginning with a telephone conference on June 7, 2018, the parties engaged in a negotiation under 42 U.S.C. § 262(*l*)(4)(A), which requires the parties to engage in "good faith negotiations" in an effort to "agree on which, if any, patents . . . shall be the subject of an action for patent infringement under [42 U.S.C. § 262(*l*)(6)]."

52. After additional communications among counsel, on June 22, 2018, the parties agreed that only the '997 Patent would be the subject of an action for patent infringement under 42 U.S.C. § 262(*l*)(6). The parties reached this agreement within 15 days of beginning their negotiations under 42 U.S.C. § 262(*l*)(4)(A).

53. Amgen Inc. filed its Complaint within the timeframe required under 42 U.S.C. § 262(*l*)(6) because Amgen Inc. filed a Complaint within 30 days after the parties reached agreement that only the '997 Patent would be the subject of an action for patent infringement under § 262(*l*)(6).

D. Defendants Receive FDA Approval for and Launch NIVESTYM™

54. On July 20, 2018, Defendants received FDA approval for NIVESTYM™ (filgrastim-aafi). Pfizer's 10-Q dated November 8, 2018 and filed with the U.S. Securities and Exchange Commission states: "Product: Nivestym (filgrastim-aafi); Indication: A biosimilar to Neupogen® (filgrastim) for all eligible indications of the reference product; Date Approved: July 2018." Exhibit 3, Pfizer's Form 10-Q, at 82; *see* Exhibit 2, "U.S. FDA Approves Pfizer's Biosimilar Nivestym™ (Filgrastim-aafi)" (July 20, 2018), https://www.pfizer.com/news/press-release/press-release- detail/u_s_fda_approves_pfizer_s_biosimilar_nivestym_filgrastim_aafi-0.

55. Pfizer stated in a press release the same day that "NIVESTYM is expected to be available in the U.S. at a significant discount to the current wholesale acquisition cost (WAC) of Neupogen." Exhibit 2.

56. Prior to launch, upon information and belief, Pfizer informed the Center for Biosimilars® that NIVESTYM™'s wholesale price would undercut Plaintiffs' wholesale price by more than 30%. Specifically, on or about October 3, 2018, in an email correspondence with Center for Biosimilars®, Pfizer indicated that "Nivestym will be priced at a wholesale acquisition cost (WAC) of $350.40 per 480-mcg prefilled syringe, a WAC that is 30.3% lower than that of the reference Neupogen, 20.3% lower than that of Zarxio (Sandoz's biosimilar filgrastim), and 14.1% lower than that of Granix (or tbo-filgrastim, Teva's follow-on filgrastim product cleared by the FDA prior to the establishment of a biosimilar approval pathway)." Exhibit 5, Kelly Davio, "Pfizer Launches Biosimilar Filgrastim, Nivestym, at a Substantial Discount," CTR. FOR BIOSIMILARS (Oct. 3, 2018), https://www.centerforbiosimilars.com/news/pfizer-launches-biosimilar-filgrastim-nivestym-at-a-substantial-discount; *see* Exhibit 6, Jessica Merrill, "Pfizer Launches Nivestym at an Aggressive Discount to Other Filgrastim Products," SCRIP (Oct. 2,

2018), https://scrip.pharmaintelligence.informa.com/SC123936/Pfizer-Launches-Nivestym-At-An-Aggressive-Discount-To-Other-Filgrastim-Products.

57. On or about July 24, 2018, on information and belief, Pfizer spokesperson Thomas Biegi stated that the launch of NIVESTYM™ would "create competition." Exhibit 7, Flora Southey, "Pfizer challenges Amgen with fourth biosimilar approval in US," BIOPHARMA-REPORTER.COM (July 24, 2018), https://www.biopharma-reporter.com/Article/2018/07/24/Pfizer-challenges-Amgen-with-fourth-biosimilar-approval-in-US.

58. Defendants' public statements evidence both price erosion and Defendants' intent to cause price erosion by infringing the '997 Patent.

59. The actions of Pfizer and Hospira are evidence of Defendants' infringement, including without limitation Defendants' offering for sale, sale, and marketing of infringing products.

60. Defendants' infringement has already injured and will continue to injure Plaintiffs including without limitation by offering for sale, selling, and marketing infringing products.

61. At least by September 24, 2018, Defendants began to sell NIVESTYM™ in the United States. FDA's National Drug Code Directory says that Nivestym™'s "Start Marketing Date" is September 24, 2018. *See* Exhibit 4, FDA NAT'L DRUG CODE DIRECTORY SEARCH RESULTS FOR "NIVESTYM" (Mar. 20, 2019).

62. Upon information and belief, NIVESTYM™ launched at a 30.3% discount to NEUPOGEN®'s wholesale acquisition cost. *See* Exhibit 5, Scrip, "Pfizer Launches Nivestym at an Aggressive Discount to Other Filgrastim Products" (Oct. 2, 2018).

63. There is a market and demand for filgrastim in the United States.

64. Plaintiffs are capable of meeting the demand for filgrastim in the United States.

65. NIVESTYM™ (filgrastim-aafi) competes with Plaintiffs' innovative product, NEUPOGEN® (filgrastim) because NIVESTYM™ (filgrastim-aafi) shares the same indication as NEUPOGEN® (filgrastim). The FDA label for NEUPOGEN® (filgrastim) states that "Neupogen is a leukocyte growth factor indicated to [d]ecrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever." *See* Exhibit 8 (FDA label for NEUPOGEN® (filgrastim)). Likewise, the FDA label for NIVESTYM™ (filgrastim-aafi) states that "Nivestym is a leukocyte growth factor indicated to [d]ecrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever." *See* Exhibit 9 (FDA label for NIVESTYM™ (filgrastim-aafi)).

66. Including Plaintiffs and Defendants, there are very few suppliers of FDA-approved filgrastim product to consumers in the United States.

67. Defendants' sales of NIVESTYM™ (filgrastim-aafi) are sales that, but for Defendants' infringement, would have been sales of NEUPOGEN® (filgrastim).

68. Additionally, Defendants' offer for sale or sale of NIVESTYM™ (filgrastim-aafi) at prices below that of NEUPOGEN® (filgrastim) erode the price of NEUPOGEN® (filgrastim).

69. Defendants' sales and marketing of NIVESTYM™ (filgrastim-aafi), including without limitation Pfizer's statements to the public such as the statements identified above and Defendants' confidential or non-confidential statements to market participants such as, without limitation, health care providers and formularies, cause Plaintiffs to lose sales of NEUPOGEN®

(filgrastim) and erode the price of NEUPOGEN® (filgrastim), and Plaintiffs are entitled to recover lost profits to compensate for this damage.

70. But for Defendants' infringement, Plaintiffs would have made additional sales of its filgrastim product, NEUPOGEN® (filgrastim), and the price of NEUPOGEN® (filgrastim) would not have been eroded by competition with Defendants' substantially-lower-priced infringing product for which Defendants did not shoulder any of the cost or burden of the years of research and development that Plaintiffs undertook to make NEUPOGEN® (filgrastim) available to patients and doctors.

71. The profits lost by Plaintiffs as a result of lost sales and price erosion caused by Defendants' infringement of the '997 Patent include at least the profits Plaintiffs would have made absent price erosion on sales of NEUPOGEN® (filgrastim) that were lost as a result of Defendants' infringement; the profits Plaintiffs would have made absent price erosion on Amgen Inc.'s own sales of NEUPOGEN® (filgrastim); and Plaintiffs' other lost profits resulting from Defendants' infringement.

THE PATENT-IN-SUIT

72. Amgen Inc. is the owner of all rights, title, and interest in U.S. Patent No. 9,643,997 ("the '997 Patent").

73. AML holds an exclusive license to the '997 Patent.

74. The '997 Patent is titled "Capture Purification Processes for Proteins Expressed in a Non-Mammalian System." The '997 Patent was duly and legally issued on May 9, 2017 by the United States Patent and Trademark Office ("USPTO"). A true and correct copy of the '997 Patent is attached to this Complaint as Exhibit 1.

75. The '997 Patent is directed to a process for purifying proteins.

CAUSES OF ACTION

FIRST COUNT
(INFRINGEMENT OF U.S. PATENT NO. 9,643,997 UNDER 35 U.S.C. § 271(e)(2)(C))

76. Plaintiffs incorporate by reference the foregoing paragraphs as if fully set forth herein.

77. On information and belief, Defendants sought FDA approval under the subsection (k) pathway to engage in the commercial manufacture, use, or sale of the Hospira Filgrastim Biosimilar Product, a proposed biosimilar version of Amgen Inc.'s NEUPOGEN® (filgrastim) product.

78. Amgen Inc. included the '997 Patent on its disclosure under 42 U.S.C. § 262(*l*)(3)(A).

79. Defendants committed an act or acts of infringement with respect to the '997 Patent under 35 U.S.C. § 271(e)(2)(C)(i) when they caused Hospira to submit the Hospira aBLA for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, or sale of the Hospira Filgrastim Biosimilar Product.

80. On information and belief, Defendants intended to manufacture, use, sell, and/or offer for sale within the United States, and/or import into the United States, the Hospira Filgrastim Biosimilar Product before the expiration of the '997 Patent.

81. Defendants have now manufactured, used, sold, and/or offered for sale within the United States, and/or imported into the United States, the Hospira Filgrastim Biosimilar Product before the expiration of the '997 Patent.

82. The manufacture, use, sale, and/or offer for sale within the United States, and/or the importation into the United States, of the Hospira Filgrastim Biosimilar Product infringes

Claims 17, 18, and 26 of the '997 Patent, literally or equivalently, under 35 U.S.C. § 271(e)(2)(C).

83. On information and belief, the manufacture, use, sale, and/or offer for sale within the United States, and/or the importation into the United States, of the Hospira Filgrastim Biosimilar Product will infringe Claims 17, 18, and 26 of the '997 Patent, literally or equivalently.

84. Representative claim 9 of the '997 Patent recites:

> A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
> (a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
> (i) a denaturant;
> (ii) a reductant; and
> (iii) a surfactant;
> (b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
> (i) a denaturant;
> (ii) an aggregation suppressor;
> (iii) a protein stabilizer; and
> (iv) a redox component;
> (c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
> (d) washing the separation matrix; and
> (e) eluting the protein from the separation matrix.

'997 Patent at 22:36-55.

85. On information and belief, the process by which Defendants manufacture the Hospira Filgrastim Biosimilar Product satisfies each limitation of Claims 17, 18, and 26 of the '997 Patent, literally or equivalently, under 35 U.S.C. § 271(e)(2)(C). With respect to the requirement that the protein is expressed in a non-native limited solubility form in a non-mammalian expression system, Defendants practice a process for purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system. With respect to

the requirement of the "solubilizing" step, in the Defendants' process, Defendants solubilize the protein in a solubilization solution comprising one or more of a denaturant, reductant, and surfactant. With respect to the requirement of the "forming" step, in the Defendants' process, Defendants form a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of a denaturant, aggregation suppressor, protein stabilizer, and redox component. With respect to the requirement of the "applying" step, Defendants apply the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix. With respect to the requirement of the "washing" step, Defendants wash the separation matrix. With respect to the requirement of the "eluting" step, Defendants elute the protein from the separation matrix.

86. Under 42 U.S.C. § 262(*l*)(3)(C), Plaintiffs have provided Defendants with a detailed statement describing the factual and legal bases of Plaintiffs' opinion that Defendants will infringe the '997 Patent through the commercial marketing of the biological product that is the subject of the Hospira aBLA. That statement provides additional details to Defendants about Plaintiffs' assertion of infringement of the '997 Patent including references to confidential information that Defendants provided to Plaintiffs under 42 U.S.C. § 262(*l*)(2). Plaintiffs do not repeat their detailed statement here because under 42 U.S.C. § 262(*l*)(1)(F), Plaintiffs are not permitted to include Defendants' confidential information provided under § 262(*l*)(2) "in any publicly-available complaint or other pleading."

87. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '997 Patent. Plaintiffs do not have an adequate remedy at law and are entitled to injunctive relief preventing Defendants from any further infringement under 35 U.S.C. § 271(e)(4)(B).

88. The manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Hospira Filgrastim Biosimilar Product before the expiration of the '997 Patent will cause and has caused injury to Plaintiffs, entitling them to damages or other monetary relief under 35 U.S.C. § 271(e)(4)(C). For example, Amgen Inc. has suffered lost profits of its NEUPOGEN® (filgrastim) product because of Defendants' infringing acts with respect to NIVESTYM™ (filgrastim-aafi), including sales of NEUPOGEN® (filgrastim) that would have been made by Plaintiffs—such as sales to and through Amgen Inc.'s wholly-owned subsidiary Amgen USA Inc.—that were either lost as a result of Defendants' infringement or were made at eroded prices because of Defendants' infringement. But for Defendants' infringement, Plaintiffs would not have suffered injury, entitling Plaintiffs to damages in the form of lost profits resulting from at least diverted sales and price erosion, and in no event less than a reasonable royalty under 35 U.S.C. § 284.

SECOND COUNT
(INFRINGEMENT OF THE '997 PATENT UNDER 35 U.S.C. § 271(g) AND DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '997 PATENT UNDER 35 U.S.C. § 271(g))

89. Plaintiffs incorporate by reference the foregoing paragraphs as if fully set forth herein.

90. Defendants sought FDA approval under the subsection (k) pathway to manufacture and sell the Hospira Filgrastim Biosimilar Product, a biosimilar version of Amgen Inc.'s NEUPOGEN® (filgrastim) product.

91. On information and belief, Defendants obtained approval to import into the United States, or offer to sell, sell, or use within the United States, the Hospira Filgrastim Biosimilar Product (NIVESTYM™) before the expiration of the '997 Patent.

92. Defendants have now manufactured, used, sold, and/or offered for sale within the United States, and/or imported into the United States, the Hospira Filgrastim Biosimilar Product before the expiration of the ’997 Patent.

93. The manufacture, use, sale, and/or offer for sale within the United States, and/or the importation into the United States, of the Hospira Filgrastim Biosimilar Product infringes Claims 17, 18, and 26 of the ’997 Patent, literally or equivalently, under 35 U.S.C. § 271(g). Specifically, Defendants’ importation into the United States or offers to sell, sales, or uses within the United States of the Hospira Filgrastim Biosimilar Product which is made by a process patented in the United States has infringed and continues to infringe Claims 17, 18, and 26 of the ’997 Patent, literally or equivalently, under 35 U.S.C. § 271(g). Thus, Plaintiffs are entitled to judgment that Defendants have infringed Claims 17, 18, and 26 of the ’997 Patent, literally or equivalently, by using, offering to sell, or selling within the United States, or importing into the United States the Hospira Filgrastim Biosimilar Product before the expiration of the ’997 Patent.

94. In addition, an actual controversy has arisen and now exists between the parties concerning whether the Hospira Filgrastim Biosimilar Product has or will infringe Claims 17, 18, and 26 of the ’997 Patent, literally or equivalently. Specifically, Defendants’ importation into the United States or offers to sell, sales, or uses within the United States of the Hospira Filgrastim Biosimilar Product which is made by a process patented in the United States will infringe Claims 17, 18, and 26 of the ’997 Patent, literally or equivalently, under 35 U.S.C. § 271(g). Thus, Plaintiffs are entitled to a declaratory judgment that Defendants have infringed or will infringe Claims 17, 18, and 26 of the ’997 Patent, literally or equivalently, by making, using, offering to sell, or selling within the United States, or importing into the United States, the Hospira Filgrastim Biosimilar Product before the expiration of the ’997 Patent.

95. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '997 Patent. Plaintiffs do not have an adequate remedy at law and are entitled to injunctive relief under 35 U.S.C. § 283 prohibiting Defendants from making, using, offering to sell, or selling within the United States, or importing into the United States, the Hospira Filgrastim Biosimilar Product before the expiration of the '997 Patent.

96. Defendants' manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Hospira Filgrastim Biosimilar Product before the expiration of the '997 Patent will cause injury to Plaintiffs, entitling them to damages under 35 U.S.C. § 284 or other monetary relief. For example, Amgen Inc. has suffered lost profits of its NEUPOGEN® (filgrastim) product because of Defendants' infringing acts with respect to NIVESTYM™ (filgrastim-aafi), including sales of NEUPOGEN® (filgrastim) that would have been made by Plaintiffs—such as sales to and through Amgen Inc.'s wholly-owned subsidiary Amgen USA Inc.—that were either lost as a result of Defendants' infringement or were made at eroded prices because of Defendants' infringement. But for Defendants' infringement, Plaintiffs would not have suffered injury, entitling Plaintiffs to damages in the form of lost profits resulting from at least diverted sales and price erosion, and in no event less than a reasonable royalty under 35 U.S.C. § 284.

97. On information and belief, Defendants' infringement of the '997 Patent is exceptional and entitles Plaintiffs to attorneys' fees and costs incurred in prosecuting this action in accordance with 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully requests that this Court enter judgment in their favor against Defendants and grant the following relief:

A. A judgment that Defendants have infringed Claims 17, 18, and 26 of the '997 Patent, literally or equivalently, under 35 U.S.C. § 271(e)(2)(C)(i);

B. A judgment that Defendants have infringed and will infringe Claims 17, 18, and 26 of the '997 Patent, literally or equivalently, under 35 U.S.C. § 271(g);

C. An order enjoining Defendants, their officers, partners, agents, servants, employees, attorneys, affiliates, divisions, subsidiaries, other related business entities, and those persons in active concert or participation with any of them, from infringing the '997 Patent, or contributing to or inducing anyone to do the same, including the manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any current or future versions of the Hospira Filgrastim Biosimilar Product, in accordance with 35 U.S.C. § 271(e)(4)(B) and 35 U.S.C. § 283;

D. A judgment compelling Defendants to pay to Plaintiffs damages adequate to compensate for Defendants' infringement or other monetary relief, in accordance with 35 U.S.C. § 271(e)(4)(C) and 35 U.S.C. § 284, in an amount to be ascertained at trial, including without limitation lost profits resulting from at least diverted sales and price erosion, and in no event less than a reasonable royalty;

E. A declaration that this is an exceptional case and awarding to Amgen its attorneys' fees and costs pursuant to 35 U.S.C. § 285; and

F. Such other relief as this Court may deem just and proper.

DEMAND FOR A JURY TRIAL

Amgen hereby demands a jury trial on all issues so triable.

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EXHIBIT 1

US009643997B2

(12) **United States Patent**
Shultz et al.

(10) **Patent No.: US 9,643,997 B2**
(45) **Date of Patent: *May 9, 2017**

(54) **CAPTURE PURIFICATION PROCESSES FOR PROTEINS EXPRESSED IN A NON-MAMMALIAN SYSTEM**

(71) Applicant: **AMGEN INC.**, Thousand Oaks, CA (US)

(72) Inventors: **Joseph Edward Shultz**, Binningen (CH); **Roger Hart**, Loveland, CO (US)

(73) Assignee: **AMGEN INC.**, Thousand Oaks, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/599,336**

(22) Filed: **Jan. 16, 2015**

(65) **Prior Publication Data**

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Related U.S. Application Data

(62) Division of application No. 12/822,990, filed on Jun. 24, 2010, now Pat. No. 8,940,878.

(60) Provisional application No. 61/220,477, filed on Jun. 25, 2009.

(51) **Int. Cl.**

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C07K 1/18	(2006.01)
C07K 1/32	(2006.01)
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(52) **U.S. Cl.**

CPC ***C07K 1/22*** (2013.01); ***C07K 1/145*** (2013.01); ***C07K 1/18*** (2013.01); ***C07K 1/32*** (2013.01); ***C07K 16/00*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(74) *Attorney, Agent, or Firm* — Raymond M. Doss

(57) **ABSTRACT**

Methods of purifying proteins expressed in non-mammalian expression systems in a non-native soluble form directly from cell lysate are disclosed. Methods of purifying proteins expressed in non-mammalian expression systems in a non-native limited solubility form directly from a refold solution are also disclosed. Resin regeneration methods are also provided.

30 Claims, 5 Drawing Sheets

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Document 260: Reply to Response to Motion re 244 Motion for Judgment on Partial Findings Pursuant to Fed. R. Civ. P. 52(c) filed by Apotex Corp., Apotex Inc. pp. 1-11; Attachments: # 1 Exhibit 1—Trial Transcript Day 2 (Jul. 12, 2016) (Willson), pp. 1-7. # 2 Exhibit 2—Trial Transcript Day 3 (Jul. 13, 2016) (Dowd), pp. 1-4. # 3 Exhibit 3—Trial Transcript Day 4 (Jul. 14, 2016) (Robinson), pp. 1-4. # 4 Exhibit 4—Trial Transcript Day 5 (Jul. 18, 2016), pp. 1-3.

Document 268: Final Judgment Signed by Judge James I. Cohn on Sep. 6, 2016. (tpl) Notice: If there are sealed documents in this case, they may be unsealed after 1 year or as directed by Court Order, unless they have been designated to be permanently sealed. See Local Rule 5.4 and Administrative Order 2014-69. (Entered: Sep. 6, 2016); pp. 1-5.

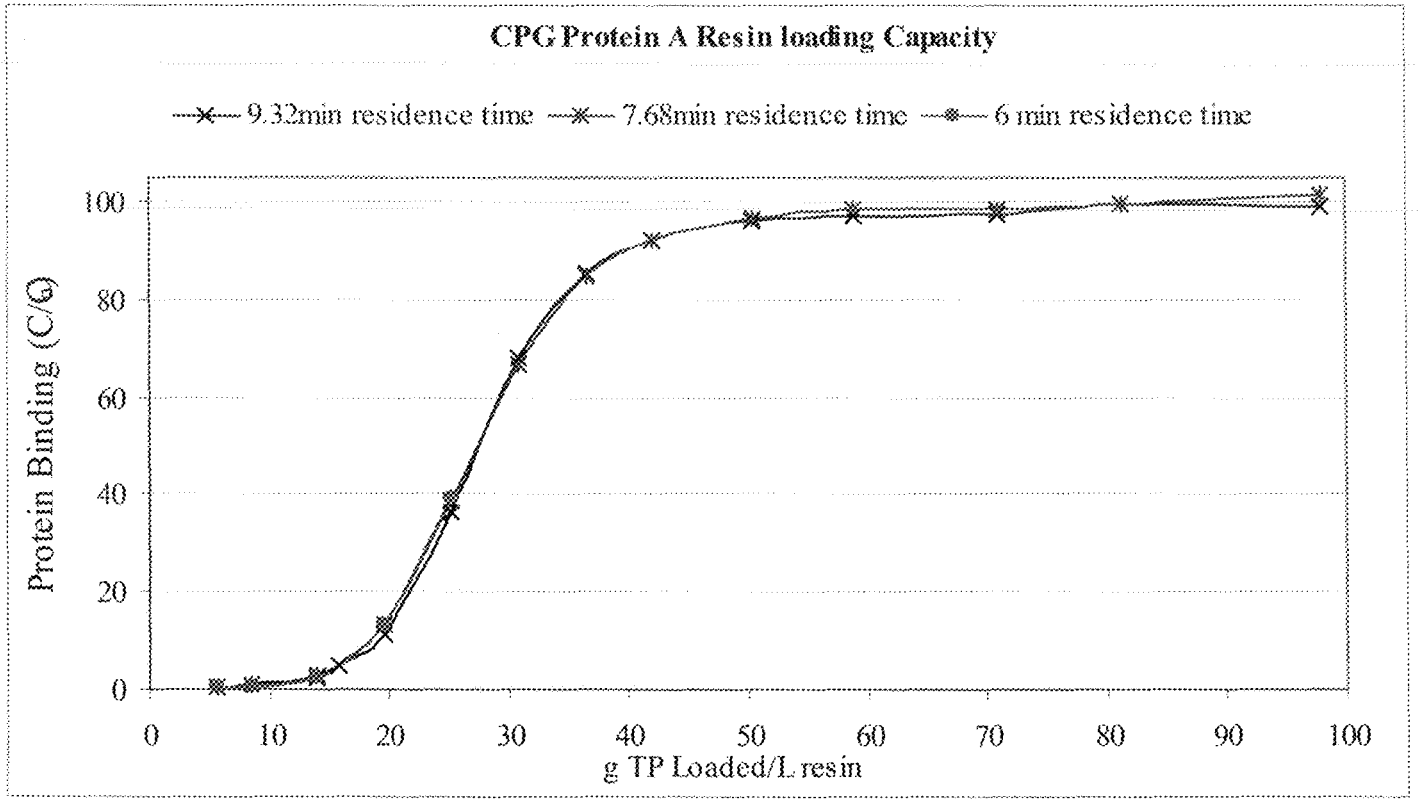
CPG Protein A Resin loading Capacity
9.32min residence time
7.68min residence time
6 min residence time
Protein Binding (C/G)
0
20
40
60
80
100
0
10
20
30
40
50
60
70
80
90
100
g TP Loaded/L resin

Figure 1

		Average Purity					
		RP-HPLC Main Peak Purity (%)	SE-HPLC Main Peak Purity (%)	CE-SDS Main Peak Purity (%)	Host Protein Level (ppm)	DNA Level (pg/mg protein)	Average Yield (%)
Load	Average (n=13)	34.5	74.5	79.2	9100.0	>70000	-
	Std. Dev (n=13)	2.4	2.7	4.4	424.3	*	-
Purified Pool	Average (n=17)	41.3	68.8	84.7	41.0	215.2	81.7
	Std. Dev (n=17)	1.5	3.8	4.0	5.7	301.2	12.3

* Data limited to N=1

Figure 2

		Average Purity					
		RP-HPLC Main Peak Purity (%)	SE-HPLC Main Peak Purity (%)	CE-SDS Main Peak Purity (%)	Host Protein Level (ppm)	DNA Level (pg/mg protein)	Average Yield (%)
Load	Average (n=5)	36.0	76.1	75.5	1400.0	>70000	-
	Std. Dev (n=5)	0.9	1.9	1.5	*	*	-
Purified Pool	Average (150 cycles)	40.2	75.0	82.4	71.4	89.2	84.3
	Std. Dev (150 cycles)	2.5	8.7	4.6	23.0	175.0	18.8

* Data limited to N=1

Figure 3

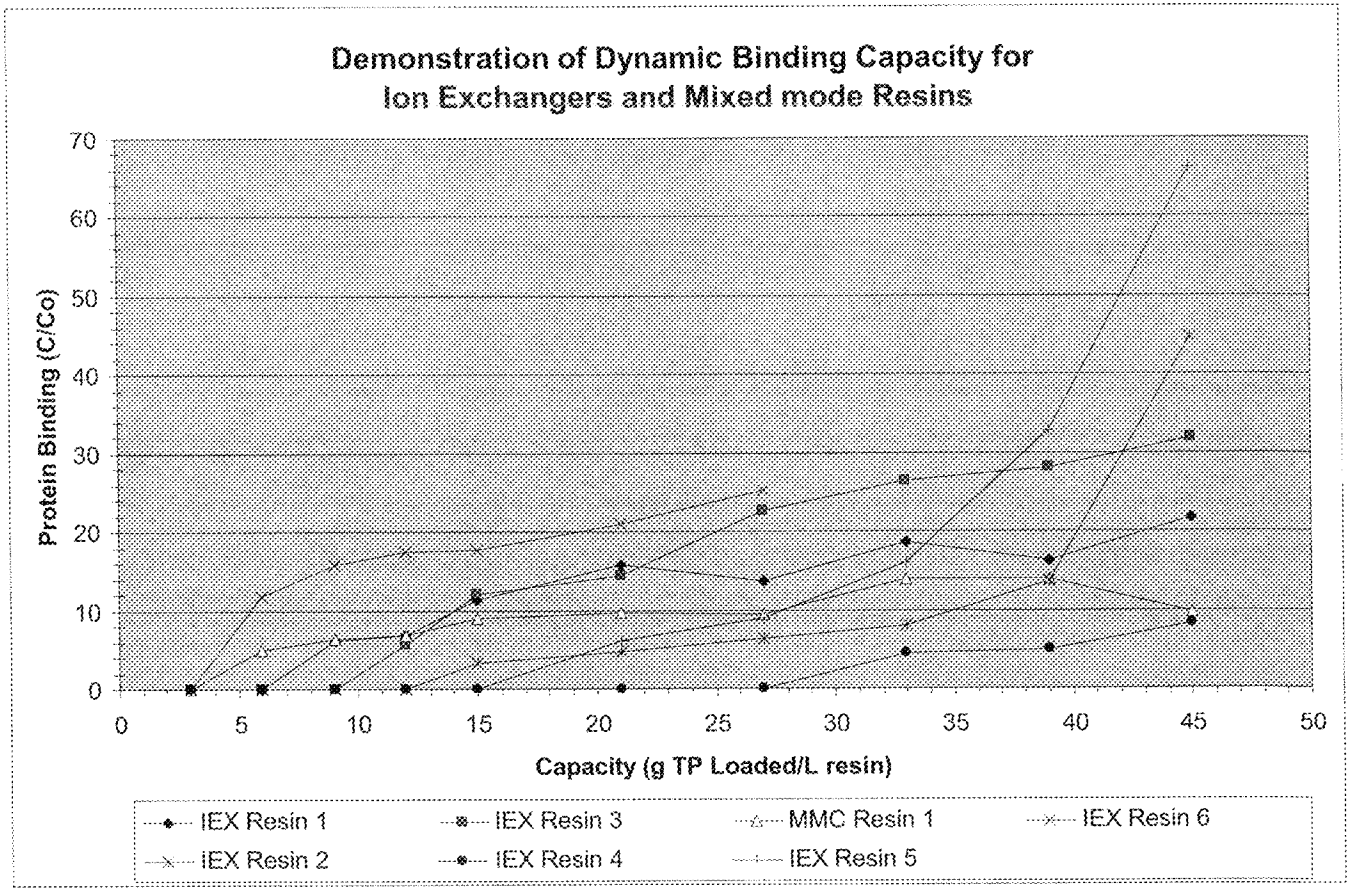
Demonstration of Dynamic Binding Capacity for Ion Exchangers and Mixed mode Resins
Protein Binding (C/Co)
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
Capacity (g TP Loaded/L resin)
IEX Resin 1
IEX Resin 3
MMC Resin 1
IEX Resin 6
IEX Resin 2
IEX Resin 4
IEX Resin 5

Figure 4

	RP-HPLC Main Peak Purity (%)	SE-HPLC Main Peak Purity (%)	Average Yield (%)
Load	29.8	64.6	-
CEX	46.0	80.3	62.0
AEX	30.9	75.7	85.0

Figure 5

CAPTURE PURIFICATION PROCESSES FOR PROTEINS EXPRESSED IN A NON-MAMMALIAN SYSTEM

This application is a divisional of U.S. application Ser. No. 12/822,990, filed on Jun. 24, 2010, now U.S. Pat. No. 8,940,878; which claims the benefit of U.S. Provisional Application No. 61/220,477 filed Jun. 25, 2009, which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates generally to processes for purifying proteins expressed in non-mammalian systems in both non-native soluble and non-native insoluble forms, and more particularly to the direct capture of such proteins from a refold mixture or a cell lysate pool by a separation matrix.

BACKGROUND OF THE INVENTION

Fc-containing proteins are typically expressed in mammalian cells, such as CHO cells. The use of affinity chromatography to purify Fc-containing proteins is documented (see, e.g., Shukla et al., (2007) *Journal of Chromatography B* 848(1):28-39) and is successful, in part, due to the degree of Fc structure observed in proteins expressed in such systems. Fc-containing proteins expressed in non-mammalian cells, however, are often deposited in the expressing cells in limited solubility forms, such as inclusion bodies, that require refolding, and this has been a limiting factor in selecting non-mammalian systems for expressing Fc-containing proteins.

A drawback to the use of Protein A, Protein G and other chemistries is that in order for a protein comprising an Fc region to associate with the Protein A or Protein G molecule, the protein needs to have a minimum amount of structure. Often, the requisite amount of structure is absent from proteins expressed recombinantly in a soluble, but non-native, form and consequently Protein A chromatography is not performed in a purification process.

In the case of a protein expressed in an insoluble non-native form, Protein A chromatography is typically not performed in a purification process until after the protein has been refolded to a degree that it can associate with the Protein A molecule and has been subsequently diluted out of its refold solution. This is because it was believed that after a protein has been refolded it was necessary to dilute or remove the components of the refold mixture in a wash step, due to the tendency of the components that typically make up a refold solution to disrupt interactions between the target protein and the Protein A molecules (Wang et al., (1997). *Biochem. J.* 325(Part 3):707-710). This dilution step can consume time and resources which, when working at a manufacturing scale of thousands of liters of culture, can be costly.

The present disclosure addresses these issues by providing simplified methods of purifying proteins comprising Fc regions that are expressed in non-mammalian expression systems in a non-native soluble form or in a non-native insoluble form.

SUMMARY OF THE INVENTION

A method of purifying a protein expressed in a non-native soluble form in a non-mammalian expression system is provided. In one embodiment the method comprises (a) lysing a non-mammalian cell in which the protein is expressed in a non-native soluble form to generate a cell lysate; (b) contacting the cell lysate with an separation matrix under conditions suitable for the protein to associate with the separation matrix; (c) washing the separation matrix; and (d) eluting the protein from the separation matrix.

The protein can be a complex protein, such as a protein is selected from the group consisting of a multimeric protein, an antibody and an Fc fusion protein. The non-mammalian expression system can comprise bacteria or yeast cells. The separation matrix can be an affinity resin, such as an affinity resin selected from the group consisting of Protein A, Protein G and a synthetic mimetic affinity resin, or it can be a non-affinity resin, such as a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin. The cell lysate can be filtered before it is contacted with the separation matrix. Although not required, the method can further comprise refolding the protein to its native form after it is eluted from the separation matrix.

A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system is provided. In one embodiment that method comprises (a) expressing a protein in a non-native limited solubility form in a non-mammalian cell; (b) lysing a non-mammalian cell; (c) solubilizing the expressed protein in a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant; (d) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component; (e) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix; (f) washing the separation matrix; and (g) eluting the protein from the separation matrix.

The non-native limited solubility form can be a component of an inclusion body. The protein can be a complex protein, such as a complex protein selected from the group consisting of a multimeric protein, an antibody, a peptibody, and an Fc fusion protein. The non-mammalian expression system can be bacteria or yeast cells. The denaturant can comprise one or more of urea, guanidinium salts, dimethyl urea, methylurea and ethylurea, the reductant can comprise one or more of cysteine, DTT, beta-mercaptoethanol and glutathione, the surfactant can comprise one or more of sarcosyl and sodium dodecylsulfate, the aggregation suppressor can be selected from the group consisting of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, tris, sodium sulfate, potassium sulfate and osmolytes, the protein stabilizer can comprise one or more of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, tris, sodium sulfate, potassium sulfate and osmolytes, and the redox component can comprise one or more of glutathione-reduced, glutathione-oxidized, cysteine, cystine, cysteamine, cystamine and beta-mercaptoethanol. The separation matrix can be an affinity resin such as an affinity resin selected from the group consisting of Protein A, Protein G, and synthetic mimetic affinity resin or the separation matrix can be a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

In other embodiments, the disclosed methods can further comprise the steps of (a) washing the separation matrix with

a regeneration reagent; and (b) regenerating the separation matrix. The regeneration reagent can be one of a strong base, such as sodium hydroxide or a strong acid, such as phosphoric acid. The regenerating can comprise washing the separation matrix with a solution comprising one or both of a chaotrope present at a concentration of 4-6 M and a reductant. The chaotrope can be one of urea, dimethyl urea, methylurea, ethylurea, and guanidinium, and the reductant can be one of cysteine, DTT, beta-mercaptoethanol and glutathione. In a particular embodiment the regenerating comprises washing the separation matrix with a solution comprising 50 mM Tris, 10 mM citrate, 6M urea, 50 mM DTT at pH 7.4.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a plot demonstrating the binding of refolded, non-mammalian non-native limited solubility fraction complex protein, to Protein A media; in the figure the X denotes resin loading at a 9.32 min residence time, star denotes resin loading at a 7.68 min residence time and solid circles denote resin loading at a 6 min residence time.

FIG. **2** is a table demonstrating purification of a complex protein comprising an Fc domain using Protein A resin.

FIG. **3** is a table demonstrating the reusability of Protein A resin when used to capture a non-mammalian non-native limited solubility complex protein over 150 cycles using the disclosed methods.

FIG. **4** is a plot demonstrating the binding profiles of a refolded, non-mammalian non-native limited solubility complex protein to six different ion exchange resins (IEX Resins 1, 2, 3, 4, 5, 6, corresponding to Toyopearl SP550C™, Toyopearl SP650M™, GigaCAP S™, POROS HS50™, Toyopearl SP650C™ and GE Healthcare SPxL™, respectively) and a mixed-mode resin (MMC Resin 1, GE Healthcare MMC™) following capture using the disclosed methods.

FIG. **5** is a table demonstrating purification levels achieved for a protein comprising an Fc domain using one anion exhange resin (Fractogel TMAE™) and one cation exchange resin (Fractogel SO_3^-™).

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides methods of capturing on a separation matrix non-native proteins produced in microbial cells. In the case of the direct capture of a protein expressed in a non-native soluble form the advantages of the present invention over typical processes include enhanced protein concentration, volume reduction, and increased recovery over traditional methods, improved protein stability, and ultimately process cost savings.

In the case of the direct capture of a protein expressed in a non-native limited solubility form, the advantages of the present invention over typical processes include the elimination of the need to dilute the protein out of a refold solution prior to capturing it on a separation matrix.

Another advantage of the disclosed methods is that they may be performed at a range of scales, from laboratory scale (typically milliliter or liter scale), a pilot plant scale (typically hundreds of liters) or on an industrial scale (typically thousands of liters). The application of the disclosed methods on large scales may be particularly desirable, due to the potential savings in time and resources.

Non-mammalian, e.g., microbial, cells can naturally produce, or can be engineered to produce, proteins that are expressed in either a soluble or a limited solubility form. Most often, engineered non-mammalian cells will deposit the recombinant proteins into large limited solubility aggregates called inclusion bodies. However, certain cell growth conditions (e.g., temperature or pH) can be modified to drive the recombinant proteins to be expressed as intracellular, soluble monomers. As an alternative to producing a protein of interest in cells in which the protein is expressed in the form of limited solubility inclusion bodies, cell growth conditions can be modified such that proteins are expressed in a non-native yet soluble form. The cells can then be lysed and the protein can be isolated by capturing it directly from cell lysate using ion exchange chromatography, affinity chromatography or mixed mode chromatography, as described herein. The method can be particularly useful for purifying proteins comprising an Fc region.

In one aspect, therefore, the present disclosure relates to a method of isolating a protein of interest comprising an Fc region that is expressed in a non-mammalian cell in a non-native, yet soluble form, from a pool of lysate generated from the cell in which the protein was expressed. The method employs a separation matrix, such as Protein A. One beneficial aspect of the disclosed method is that it eliminates the need for a refolding step before the protein is applied to the separation matrix. That is, non-mammalian cells expressing the protein of interest in a non-native soluble form can be lysed, the lysate applied directly to the separation matrix and the protein subsequently eluted from the separation matrix. This process allows the separation of proteins from cell cultures in highly concentrated pools that can be subsequently refolded at high concentrations and can be of benefit when producing large quantities of protein, particularly since the method is scalable from bench scale, which involves cultures on the order of several liters, up to production scale, which involves cultures of thousands of liters.

Following isolation by the separation matrix, the protein of interest can optionally be subsequently refolded using any technique known or suspected to work well for the protein of interest.

In another aspect, the present invention relates to a method of isolating a protein of interest comprising an Fc region that is expressed in a non-native limited solubility form, for example in inclusion bodies, that needs to be refolded and isolated from the refold mixture. Commonly, a refold solution contains a denaturant (e.g., urea or other chaotrope, organic solvent or strong detergent), an aggregation suppressor (e.g., a mild detergent, arginine or low concentrations of PEG), a protein stabilizer (e.g., glycerol, sucrose or other osmolyte, salts) and/or a redox component (e.g., cysteine, cystine, cystamine, cysteamine, glutathione). While often beneficial for refolding proteins, these components can inhibit purification (see, e.g., Wang et al., (1997) *Biochemical Journal* 325 (Part 3):707-710) and it is necessary to isolate or dilute the protein from these components for further processing, particularly before applying the protein to a separation matrix.

In one embodiment of the disclosed method, purification is achieved by directly applying a protein of interest, which is present in a refold mixture, to a separation matrix. In this approach, following a refold step the entire refold mixture, including the protein of interest, is applied directly to a separation matrix, such as a Protein A or G resin. The protein of interest associates with the matrix in the presence of the components of refold buffer, impurities are washed away and the protein is eluted. Since the method omits the need for removing any components of the refold mixture before the

refold mixture is applied to a separation matrix, the method can have the effect of saving steps, time and resources that are typically expended on removing the protein from refolding and dilution buffers in purification processes. In some cases, the method can also reduce or eliminate the need for subsequent purification steps.

The disclosed methods can also be employed to purify proteins expressed in a non-native soluble and non-native limited solubility forms in a non-mammalian expression system that have subsequently been derivatized. For example, following expression a protein comprising an Fc region can be associated with a small molecule, such as a toxin. Such conjugates can be purified using the methods described herein.

I. DEFINITIONS

As used herein, the terms "a" and "an" mean one or more unless specifically indicated otherwise.

As used herein, the term "non-mammalian expression system" means a system for expressing proteins in cells derived from an organism other than a mammal, including but not limited to, prokaryotes, including bacteria such as *E. coli*, and yeast. Often a non-mammalian expression system is employed to express a recombinant protein of interest, while in other instances a protein of interest is an endogenous protein that is expressed by a non-mammalian cell. For purposes of the present disclosure, regardless of whether a protein of interest is endogenous or recombinant, if the protein is expressed in a non-mammalian cell then that cell is a "non-mammalian expression system." Similarly, a "non-mammalian cell" is a cell derived from an organism other than a mammal, examples of which include bacteria or yeast.

As used herein, the term "denaturant" means any compound having the ability to remove some or all of a protein's secondary and tertiary structure when placed in contact with the protein. The term denaturant refers to particular chemical compounds that affect denaturation, as well as solutions comprising a particular compound that affect denaturation. Examples of denaturants that can be employed in the disclosed method include, but are not limited to urea, guanidinium salts, dimethyl urea, methylurea, ethylurea and combinations thereof.

As used herein, the term "aggregation suppressor" means any compound having the ability to disrupt and decrease or eliminate interactions between two or more proteins. Examples of aggregation suppressors can include, but are not limited to, amino acids such as arginine, proline, and glycine; polyols and sugars such as glycerol, sorbitol, sucrose, and trehalose; surfactants such as, polysorbate-20, CHAPS, Triton X-100, and dodecyl maltoside; and combinations thereof.

As used herein, the term "protein stabilizer" means any compound having the ability to change a protein's reaction equilibrium state, such that the native state of the protein is improved or favored. Examples of protein stabilizers can include, but are not limited to, sugars and polyhedric alcohols such as glycerol or sorbitol; polymers such as polyethylene glycol (PEG) and α-cyclodextrin; amino acids salts such as arginine, proline, and glycine; osmolytes and certain Hoffmeister salts such as Tris, sodium sulfate and potassium sulfate; and combinations thereof.

As used herein, the terms "Fc" and "Fc region" are used interchangeably and mean a fragment of an antibody that comprises human or non-human (e.g., murine) C_{H2} and C_{H3} immunoglobulin domains, or which comprises two contiguous regions which are at least 90% identical to human or non-human C_{H2} and C_{H3} immunoglobulin domains. An Fc can but need not have the ability to interact with an Fc receptor. See, e.g., Hasemann & Capra, "Immunoglobulins: Structure and Function," in William E. Paul, ed., *Fundamental Immunology*, Second Edition, 209, 210-218 (1989), which is incorporated by reference herein in its entirety.

As used herein, the terms "protein" and "polypeptide" are used interchangeably and mean any chain of at least five naturally or non-naturally occurring amino acids linked by peptide bonds.

As used herein, the term "complex molecule" means any protein that is (a) larger than 20,000 MW, or comprises greater than 250 amino acid residues, and (b) comprises two or more disulfide bonds in its native form. A complex molecule can, but need not, form multimers. Examples of complex molecules include but are not limited to, antibodies, peptibodies and polypeptides comprising an Fc domain and other large proteins. Peptibodies are described in U.S. Pat. No. 6,660,843, U.S. Pat. No. 7,138,370 and U.S. Pat. No. 7,511,012.

As used herein, the term "peptibody" refers to a polypeptide comprising one or more bioactive peptides joined together, optionally via linkers, with an Fc domain. See U.S. Pat. No. 6,660,843, U.S. Pat. No. 7,138,370 and U.S. Pat. No. 7,511,012 for examples of peptibodies.

As used herein, the terms "Fc fusion" and "Fc fusion protein" are used interchangeably and refer to a peptide or polypeptide covalently attached to an Fc domain.

As used herein the term "Protein A" means any protein identical or substantially similar to Staphylococcal Protein A, including commercially available and/or recombinant forms of Protein A. For the purposes of this invention, Protein A specifically includes engineered Protein A derived media, such as Mab Select SuRe™ media (GE Healthcare), in which a single subunit (e.g., the B subunit) is replicated two or more times and joined in a contiguous sequence to form a recombinant Protein A molecule, and other non-naturally occurring Protein A molecules.

As used herein, the term "Protein G" means any protein identical or substantially similar to Streptococcal Protein G, including commercially available and/or recombinant forms of Protein G.

As used herein, the term "substantially similar," when used in the context of a protein, including Protein A, means proteins that are at least 80%, preferably at least 90% identical to each other in amino acid sequence and maintain or alter in a desirable manner the biological activity of the unaltered protein. Included in amino acids considered identical for the purpose of determining whether proteins are substantially similar are amino acids that are conservative substitutions, unlikely to affect biological activity, including the following: Ala for Ser, Val for Ile, Asp for Glu, Thr for Ser, Ala for Gly, Ala for Thr, Ser for Asn, Ala for Val, Ser for Gly, Tyr for Phe, Ala for Pro, Lys for Arg, Asp for Asn, Leu for Ile, Leu for Val, Ala for Glu, Asp for Gly, and these changes in the reverse. See, e.g., Neurath et al., *The Proteins*, Academic Press, New York (1979). The percent identity of two amino sequences can be determined by visual inspection and mathematical calculation, or more preferably, the comparison is done by comparing sequence information using a computer program such as the Genetics Computer Group (GCG; Madison, Wis.) Wisconsin package version 10.0 program, "GAP" (Devereux et al., 1984, *Nucl. Acids Res.* 12: 387) or other comparable computer programs. The preferred default parameters for the "GAP" program includes: (1) the weighted amino acid comparison matrix of

Gribskov and Burgess ((1986), *Nucl. Acids Res.* 14: 6745), as described by Schwartz and Dayhoff, eds., *Atlas of Polypeptide Sequence and Structure,* National Biomedical Research Foundation, pp. 353-358 (1979), or other comparable comparison matrices; (2) a penalty of 30 for each gap and an additional penalty of 1 for each symbol in each gap for amino acid sequences; (3) no penalty for end gaps; and (4) no maximum penalty for long gaps. Other programs used by those skilled in the art of sequence comparison can also be used.

As used herein, the terms "isolate" and "purify" are used interchangeably and mean to reduce by 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%, or more, the amount of heterogenous elements, for example biological macromolecules such as proteins or DNA, that may be present in a sample comprising a protein of interest. The presence of heterogenous proteins can be assayed by any appropriate method including High-performance Liquid Chromatography (HPLC), gel electrophoresis and staining and/or ELISA assay. The presence of DNA and other nucleic acids can be assayed by any appropriate method including gel electrophoresis and staining and/or assays employing polymerase chain reaction.

As used herein, the term "separation matrix" means any adsorbent material that utilizes specific, reversible interactions between synthetic and/or biomolecules, e.g., the property of Protein A to bind to an Fc region of an IgG antibody or other Fc-containing protein, in order to effect the separation of the protein from its environment. In other embodiments the specific, reversible interactions can be base on a property such as isoelectric point, hydrophobicity, or size. In one particular embodiment, a separation matrix comprises an adsorbent, such as Protein A, affixed to a solid support. See, e.g., Ostrove (1990) in "Guide to Protein Purification," *Methods in Enzymology* 182: 357-379, which is incorporated herein in its entirety.

As used herein, the terms "non-native" and "non-native form" are used interchangeably and when used in the context of a protein of interest, such as a protein comprising a Fc domain, mean that the protein lacks at least one formed structure attribute found in a form of the protein that is biologically active in an appropriate in vivo or in vitro assay designed to assess the protein's biological activity. Examples of structural features that can be lacking in a non-native form of a protein can include, but are not limited to, a disulfide bond, quaternary structure, disrupted secondary or tertiary structure or a state that makes the protein biologically inactive in an appropriate assay. A protein in a non-native form can but need not form aggregates.

As used herein, the term "non-native soluble form" when used in the context of a protein of interest, such as a protein comprising a Fc domain, means that the protein lacks at least one formed structure attribute found in a form of the protein that is biologically active in an appropriate in vivo or in vitro assay designed to assess the protein's biological activity, but in which the protein is expressed in a form or state that is soluble intracellularly (for example in the cell's cytoplasm) or extracellularly (for example, in a lysate pool).

As used herein, the term "non-native limited solubility form" when used in the context of a protein of interest, such as a protein comprising a Fc domain, means any form or state in which the protein lacks at least one formed structural feature found in a form of the protein that (a) is biologically active in an appropriate in vivo or in vitro assay designed to assess the protein's biological activity and/or (b) forms aggregates that require treatment, such as chemical treatment, to become soluble. The term specifically includes proteins existing in inclusion bodies, such as those sometimes found when a recombinant protein is expressed in a non-mammalian expression system.

As used herein, the term "soluble form" when used in the context of a protein of interest, such as a protein comprising a Fc domain, broadly refers to a form or state in which the protein is expressed in a form that is soluble in a intracellularly (for example in the cell's cytoplasm) or extracellularly (for example, in a cell lysate pool).

II. DIRECT CAPTURE OF A PROTEIN EXPRESSED IN A NON-NATIVE SOLUBLE FORM IN A NON-MAMMALIAN EXPRESSION SYSTEM

One advantage of the disclosed method over typical purification methods is the elimination of the need for a refolding step before the soluble protein is applied to the separation matrix. That is, a protein solublized in cell lysate can be directly applied to the separation matrix. This is advantageous because the method does not require any initial purification efforts, although an initial filtration step may be desirable in some cases.

In the case of a protein comprising a Fc domain, the Fc region must have a certain level of structure to be bound by protein A, (Wang et al., (1997) *Biochem. J.* 325(Part 3):707-710). This fact has limited the application of separation matrices for purifying proteins that are expressed in a non-native soluble form, particularly proteins comprising an Fc region, because it is commonly believed that a soluble non-native Fc-containing protein would not have the requisite structural elements required to associate with a separation matrix. Furthermore, the Fc region of an antibody spontaneously forms a homodimer under non-reducing conditions and prior to the instant disclosure it was unexpected to observe that even in the reductive environment of the cell, the Fc-conjugated proteins and peptides not only form enough structure for protein to bind to the affinity resin, but that the individual peptide chains readily formed non-covalent dimers, even though the proteins had not yet been completely refolded to native form.

In view of prevailing beliefs, the success of the disclosed method was surprising and unanticipated because it was not expected that a non-mammalian, microbial cell fermentation could be induced to produce a protein that was soluble, yet still had enough structure to associate with the affinity separation matrix.

The disclosed method can be employed to purify a protein of interest that is expressed in a non-native soluble form in a non-mammalian cell expression system. The protein of interest can be produced by living host cells that either naturally produce the protein or that have been genetically engineered to produce the protein. Methods of genetically engineering cells to produce proteins are known in the art. See, e.g., Ausabel et al., eds. (1990), *Current Protocols in Molecular Biology* (Wiley, New York). Such methods include introducing nucleic acids that encode and allow expression of the protein into living host cells. In the context of the present disclosure, a host cell will be a non-mammalian cell, such as bacterial cells, fungal cells, yeast cells, and insect cells. Bacterial host cells include, but are not limited to, *Escherichia coli* cells. Examples of suitable *E. coli* strains include: HB101, DH5α, GM2929, JM109, KW251, NM538, NM539, and any *E. coli* strain that fails to cleave foreign DNA. Fungal host cells that can be used include, but are not limited to, *Saccharomyces cerevisiae, Pichia pasto-*

ris and *Aspergillus* cells. New cell lines can be established using methods known to those skilled in the art (e.g., by transformation, viral infection, and/or selection). It is noted that the method can be performed on proteins that are endogenously expressed by the non-mammalian cell as well.

During the production of a non-mammalian culture, growth conditions can be identified and employed so as to favor the production of a protein of interest in an intracellular soluble form. Such conditions can be identified by systematic empirical optimization of the culture condition parameters, such as temperature or pH. This optimization can be achieved using analysis of multifactorial matrices. For example, a matrix or series of multifactorial matrices can be evaluated to optimize temperature and pH conditions favor production of a desired species (i.e., a non-native soluble form). An optimization screen can be set up to systematically evaluate temperature and pH in a full or partial factorial matrix, with each component varied over a range of at least three temperature or pH levels with all other parameters kept constant. The protein can be expressed and the yield and quality of protein expressed in the desired form can be evaluated using standard multivariate statistical tools.

Initially, non-mammalian cells that express a particular protein of interest are grown to a desired target density under conditions designed to induce expression of the protein in a soluble form. In one embodiment, the cells express a wild type protein of interest. In another embodiment, the cells can be engineered using standard molecular biology techniques to recombinantly express a protein of interest, and induced to produce the protein of interest. The protein of interest can be any protein, for example a protein that comprises an Fc moiety. Such a protein can be, for example, an antibody, a peptibody or an Fc fusion protein, any of which can be joined to an Fc moiety via a linker.

Once the desired target density is reached, the non-mammalian cells are separated from the growth media. One convenient way of achieving separation is by centrifugation, however filtration and other clarification methods can also be used.

The cells are then collected and are resuspended to an appropriate volume in a resuspension solution. Examples of resuspension solutions that can be used in the disclosed methods include phosphate buffered saline, Tris buffered saline, or water. The selection of an appropriate buffer will be determined, in part, by the properties of the molecule of interest as well as any volume or concentration constraints.

Following resuspension, the non-mammalian cells are lysed to release the protein, which will be present in the cell lysate in a non-native soluble form to generate a cell lysate. The lysis can be performed using any convenient means, such as feeding the cell suspension through a high pressure homogenizer or by employing a chemical lysis process. Whichever lytic process is selected, the function of the lysis step is to break open the cells and to break down DNA. The lysis can be performed in multiple cycles to achieve a more complete lysis or to accommodate large volumes of cell suspension. For example, the cell suspension can be fed through a mechanical homogenizer several times. This process releases the intracellular contents, including the protein of interest, and forms a pool of cell lysate.

Following the lysis procedure, the cell lysate can optionally be filtered. Filtration can remove particulate matter and/or impurities, such as nucleic acids and lipids, and may be desirable in some cases, such as when one suspects that direct application of the cell lysate to the chromatography equipment or media may lead to fouling or clogging, or when the separation matrix is sensitive to fouling or difficult to clean in-place. The benefit of filtering the cell lysate prior to contacting it with the separation matrix can be determined on a case-by-case basis.

After the lysis procedure, the cell lysate can optionally be incubated for an appropriate amount of time in the presence of air or oxygen, or exposed to a redox component or redox thiol-pair. The incubation can facilitate and/or ensure the formation of the minimal secondary structure required to facilitate an association with a separation matrix. The particular length of the incubation can vary with the protein but is typically less than 72 hours (e.g., 0, 0.5, 1, 2, 3, 5, 7, 10, 12, 18, 24, 36, 48 or 72 hours). When an incubation is performed, the length of incubation time can be determined by empirical analysis for each protein, which in some cases will be shorter (or omitted) and other cases longer.

Following the incubation period the cell lysate, which comprises the released protein of interest, is contacted with a separation matrix under conditions suitable for the protein to associate with a binding element of the separation matrix. Representative conditions conducive to the association of a protein with an affinity matrix are provided in the Examples. The separation matrix can be any media by which the protein of interest can be separated from the components of the resuspension and/or lysis buffer, including impurities such as host cell proteins, DNA, lipids and chemical impurities introduced by the components of the resuspension and/or lysis buffer.

Proteins A and G are often employed to purify antibodies, peptibodies and other fusion proteins comprising a Fc region by affinity chromatography. See, e.g., Vola et al. (1994), *Cell Biophys.* 24-25: 27-36; Aybay and Imir (2000), *J. Immunol. Methods* 233(1-2): 77-81; Ford et al. (2001), *J. Chromatogr. B* 754: 427-435. Proteins A and G are useful in this regard because they bind to the Fc region of these types of proteins. Recombinant fusion proteins comprising an Fc region of an IgG antibody can be purified using similar methods. Proteins A and G can be employed in the disclosed methods as an adsorbent component of a separation matrix.

Thus, examples of separation matrices that can be employed in the present invention include Protein A resin, which is known to be, and is commonly employed as, an effective agent for purifying molecules comprising an Fc moiety, as well as Protein G and synthetic mimetic affinity resins, such as MEP HyperCel® chromatography resin.

After the protein of interest has been associated with the separation matrix by contacting the cell lysate containing the protein with the separation matrix, thereby allowing the protein to associate with the adsorbent component of the separation matrix, the separation matrix is washed to remove unbound lysate and impurities.

The wash buffer can be of any composition, as long as the composition and pH of the wash buffer is compatible with both the protein and the matrix, and maintains the interaction between the protein and the matrix. Examples of suitable wash buffers that can be employed include solutions containing glycine, Tris, citrate, or phosphate; typically at levels of 5-100 mM (e.g., 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75 or 100 mM). These solutions can also contain an appropriate salt ion, such as chloride, sulfate or acetate at levels of 5-500 mM (e.g., 5, 10, 12, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450 or 500 mM). The resin can be washed once or any number of times. The exact composition of a wash buffer will vary with the protein being purified.

After the separation matrix with which the protein has associated has been washed, the protein of interest is eluted from the matrix using an appropriate solution. The protein of interest can be eluted using a solution that interferes with the

binding of the adsorbent component of the separation matrix to the protein, for example by disrupting the interactions between the separation matrix and the protein of interest. This solution can include an agent that can either increase or decrease pH, and/or a salt. For example, the pH can be lowered to about 4.5 or less, for example to between about 3.3 and about 4.0, e.g., 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4 or 4.5. A solution comprising citrate or acetate, for example, can be employed to lower the pH. Other methods of elution are also known, such as via the use of chaotropes (see, e.g., Ejima et al. (2005) *Analytical Biochemistry* 345(2):250-257) or amino acid salts (see, e.g., Arakawa et al. (2004) *Protein Expression & Purification* 36(2):244-248). Protocols for such affinity chromatography are well known in the art. See, e.g., Miller and Stone (1978), *J. Immunol. Methods* 24(1-2): 111-125. Conditions for binding and eluting can be readily optimized by those skilled in the art. The exact composition of an elution buffer will vary with the protein being purified. The protein can then optionally be further purified from the elution pool and refolded as necessary. In other situations the protein need not be further purified and instead can be refolded directly from the elution pool. Refolding directly from the elution pool may or may not require denaturation or reduction of the protein prior to incubation in a refolding solution and will depend in part on the properties of the protein.

In some cases it will be desirable to provide the separation matrix in a column format. In such cases a chromatography column can be prepared and then equilibrated before the cell suspension is loaded. Techniques for generating a chromatography column are well known and can be employed. An optional preparation and equilibration step can comprise washing the column with a buffer having an appropriate pH and salt condition that is conducive to protein-matrix interactions. This step can provide the benefit of removing impurities present in the separation matrix and can enhance the binding of the protein to be isolated to the adsorbent component of a separation matrix.

As noted, the separation matrix can be disposed in a column. The column can be run with or without pressure and from top to bottom or bottom to top. The direction of the flow of fluid in the column can be reversed during the purification process. Purifications can also be carried out using a batch process in which the solid support is separated from the liquid used to load, wash, and elute the sample by any suitable means, including gravity, centrifugation, or filtration. Moreover, purifications can also be carried out by contacting the sample with a filter that adsorbs or retains some molecules in the sample more strongly than others, such as anion exchange membrane chromatography.

If desired, the protein concentration of a sample at any given step of the disclosed method can be determined, and any suitable method can be employed. Such methods are well known in the art and include: 1) colorimetric methods such as the Lowry assay, the Bradford assay, the Smith assay, and the colloidal gold assay; 2) methods utilizing the UV absorption properties of proteins; and 3) visual estimation based on stained protein bands on gels relying on comparison with protein standards of known quantity on the same gel. See, e.g., Stoschek (1990), "Quantitation of Protein," in "Guide to Protein Purification," *Methods in Enzymology* 182: 50-68. Periodic determinations of protein concentration can be useful for monitoring the progress of the method as it is performed.

It is noted that any or all steps of the disclosed methods can be carried out manually or by any convenient automated means, such as by employing automated or computer-controlled systems.

III. DIRECT CAPTURE OF NON-NATIVE LIMITED SOLUBILITY PROTEIN FORMS FROM A REFOLD SOLUTION FOLLOWING EXPRESSION IN NON-MAMMALIAN CELLS

In another aspect of the present disclosure, a method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system is disclosed. An advantage of the disclosed method is that the method eliminates the need for removing or diluting the refold solution before applying the protein to a separation matrix, thereby saving the time and resources associated with what is a typical step in a purification process for isolating proteins expressed in a non-native limited solubility form.

Non-mammalian cells, e.g., microbial cells, can produce recombinant proteins that are expressed intracellularly in either a soluble or a limited solubility form. When the growth conditions are not directed to force expression of the protein in a soluble form, the cells may deposit the recombinant proteins into large relatively insoluble aggregates, such as inclusion bodies. These aggregates comprise protein that is typically not biologically active or less active than the completely folded native form of the protein. In order to produce a functional protein, these inclusion bodies often need to be carefully denatured so that the protein of interest can be extracted and refolded into a biologically active form.

In typical approaches, the inclusion bodies need to be captured, washed, exposed to a denaturing and/or reducing solubilization solution and the denaturing solution is then diluted with a solution to generate a condition that allows the protein to refold into an active form and form a structure that is found in the native protein. Subsequently, it is necessary to remove the components of the diluted denaturing solution from the immediate location of the protein. In order to do this, the refold solution comprising the solubilization solution and the refolded protein is typically diluted with a buffered solution before it is applied to a separation matrix, such as a Protein A ion exchange or other mixed-mode adsorbents. This process can be time-consuming and resource-intensive. It also significantly increases the volumes that need to be handled, as well as the associated tankage requirements, which can become limiting when working on large scales. The disclosed method eliminates the need for such a dilution step

The disclosed method is particularly useful for purifying a protein of interest that is expressed in a non-native limited solubility form in a non-mammalian cell expression system. The protein of interest can be produced by living host cells that either naturally produce the protein or that have been genetically engineered to produce the protein. Methods of genetically engineering cells to produce proteins are well known in the art. See, e.g., Ausabel et al., eds. (1990), *Current Protocols in Molecular Biology* (Wiley, New York). Such methods include introducing nucleic acids that encode and allow expression of the protein into living host cells. In the context of the present disclosure, these host cells will be non-mammalian cells, such as bacterial cells, fungal cells. Bacterial host cells include, but are not limited to *Escherichia coli* cells. Examples of suitable *E. coli* strains include: HB101, DH5α, GM2929, JM109, KW251, NM538, NM539, and any *E. coli* strain that fails to cleave foreign

DNA. Fungal host cells that can be used include, but are not limited to, *Saccharomyces cerevisiae, Pichia pastoris* and *Aspergillus* cells. New cell lines can be established using methods well know by those skilled in the art (e.g., by transformation, viral infection, and/or selection). It is noted that the method can be performed on endogenous proteins that are naturally expressed by the non-mammalian cell as well.

Initially, non-mammalian cells that express a particular protein of interest are grown to a desired target density. In one embodiment, the cells can be expressing a particular wild type microbial protein of interest. In another embodiment, the cells can be engineered using standard molecular biology techniques to recombinantly express a protein of interest, and in this context they can be induced to overproduce the protein of interest. The protein of interest can be any protein, for example a protein that comprises an Fc moiety. Such a protein can be, for example, an antibody, a peptibody or an Fc fusion protein, any of which can be joined to an Fc moiety via a linker.

Once the desired target density is reached, the non-mammalian cells can be separated from the growth media. One convenient way of achieving separation is by centrifugation, however filtration and other clarification methods can also be used.

The cells are then collected and are resuspended to an appropriate volume in a resuspension solution. Examples of resuspension solutions that can be used in the present invention include phosphate-buffered saline, Tris-buffered saline, or water. The selection of an appropriate buffer will be determined, in part, by the properties of the molecule of interest as well as any volume or concentration constraints.

In order to release the limited solubility non-native protein from the cells, the non-mammalian cells are lysed to form a cell lysate comprising the released the limited solubility non-native protein. The lysis can be performed in any convenient way, such as feeding the cell suspension through a high pressure homogenizer or by employing a chemical lysis process. Whichever lysis process is selected, the function of the lysis step is to break open the cells and to break down DNA. The lysis can be performed in multiple cycles to achieve a more complete lysis or to accommodate large volumes of cell suspension. For example, the cell suspension can be fed through a mechanical homogenizer several times. This process releases the intracellular contents, including the naturally-occurring or recombinant protein of interest, and forms a pool of cell lysate.

Next, the limited solubility non-native protein is separated from the rest of the lysis pool. This can be done, for example, by centrifugation. Representative conditions for a centrifuge-mediated separation or washing typically include removal of excess water from the cell lysate, resuspension of the resulting slurry in a resuspension solution. This washing process may be performed once or multiple times. Examples of typical centrifuge types include, but are not limited to, disk-stack, continuous discharge, and tube bowl. Examples of resuspension solutions that can be used in the present invention include phosphate-buffered saline, Tris-buffered saline, or water and can include other agents, such as ETDA or other salts. The selection of an appropriate buffer will be determined, in part, by the properties of the molecule of interest as well as any volume or concentration constraints. The exact composition of an resuspension buffer will vary with the protein being purified.

The expressed protein is then solubilized in a solubilization solution comprising one or more of (i) a denaturant, (ii) a reductant and (iii) a surfactant. The denaturant can be included as a means of unfolding the limited solubility protein, thereby removing any existing structure, exposing buried residues and making the protein more soluble.

Any denaturant can be employed in the solubilization solution. Examples of some common denaturants that can be employed in the refold buffer include urea, guanidinium, dimethyl urea, methylurea, or ethylurea. The specific concentration of the denaturant can be determined by routine optimization.

The reductant can be included as a means to reduce exposed residues that have a propensity to form covalent intra or intermolecular-protein bonds and minimize non-specific bond formation. Examples of suitable reductants include, but are not limited to, cysteine, DTT, beta-mercaptoethanol and glutathione. The specific concentration of the reductant can be determined by routine optimization.

A surfactant can be included as a means of unfolding the limited solubility non-native protein, thereby exposing buried residues and making the protein more soluble. Examples of suitable surfactants include, but are not limited to, sarcosyl and sodium dodecylsulfate. The specific concentration of the surfactant can be determined by routine optimization.

Although the composition of a solubilization solution will vary with the protein being purified, in one particular embodiment the solubilization solution comprises 4-6 M guanidine, 50 mM DTT.

Continuing, a refold solution comprising the solubilization solution (which comprises the protein), and a refold buffer is formed. The refold buffer comprises one or more of (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component. The denaturant can be included as a means of modifying the thermodynamics of the solution, thereby shifting the equilibrium towards an optimal balance of native form. The aggregation suppressor can be included as a means of preventing non-specific association of one protein with another, or with one region of a protein with another region of the same protein. The protein stabilizer can be included as a means of promoting stable native protein structure and may also suppress aggregation.

In various embodiments, the denaturant in the refold buffer can be selected from the group consisting of urea, guanidinium salts, dimethyl urea, methylurea and ethylurea.

In various embodiments, the protein stabilizer in the refold buffer can be selected from the group consisting of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes.

In various embodiments, the aggregation suppressor can be selected from the group consisting of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes.

In various embodiments, the thiol-pairs can comprise at least one component selected from the group consisting of glutathione-reduced, glutathione-oxidized, cysteine, cystine, cysteamine, cystamine and beta-mercaptoethanol.

The specific concentrations of the components of a refold buffer can be determined by routine optimization. For example, a matrix or series of multifactorial matrices can be evaluated to optimize the refolding buffer for conditions that optimize yield and distributions of desired species. An optimization screen can be set up to systematically evaluate denaturant, aggregation suppressor, protein stabilizer and redox component concentrations and proportions in a full or partial factorial matrix, with each component varied over a

range of concentrations with all other parameters kept constant. The completed reactions can be evaluated by RP-HPLC and SE-HPLC analysis for yield and product quality using standard multivariate statistical tools.

The function of the buffer component of the refold solution is to maintain the pH of the refold solution and can comprise any buffer that buffers in the appropriate pH range. Examples of the buffering component of a refold buffer that can be employed in the method include, but are not limited to, phosphate buffers, citrate buffers, tris buffer, glycine buffer, CHAPS, CHES, and arginine-based buffers, typically at levels of 5-100 mM (e.g., 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75 80, 85, 90, 95 or 100, mM).

Although the composition of an refold buffer will vary with the protein being purified, in one embodiment a refold buffer comprises arginine, urea, glycerol, cysteine and cystamine.

The refold solution can then be incubated for a desired period of time. The incubation period can be of any length but is typically between 0 and 72 hours (e.g., 0, 0.5, 1, 2, 3, 5, 7, 10, 12, 18, 24, 36, 48 or 72 hours).

After an appropriate incubation time, the refold solution is then applied to a separation matrix under conditions suitable for the protein to associate with the matrix. The separation matrix can be any media by which the protein of interest can be separated from the components of the resuspension and/or lysis buffer, including impurities such as host cell proteins, DNA and chemical impurities introduced by the components of the solubilization and/or lysis buffer.

Proteins A and G are often employed to purify antibodies, peptibodies and other fusion proteins comprising a Fc region by affinity chromatography. See, e.g., Vola et al. (1994), *Cell Biophys.* 24-25: 27-36; Aybay and Imir (2000), *J. Immunol. Methods* 233(1-2): 77-81; Ford et al. (2001), *J. Chromatogr. B* 754: 427-435. Proteins A and G are useful in this regard because they bind to the Fc region of these types of proteins. Recombinant fusion proteins comprising an Fc region of an IgG antibody can be purified using similar methods. Proteins A and G can be employed in the disclosed methods as an adsorbent component of a separation matrix.

Thus, examples of affinity separation matrices that can be employed in the present invention include Protein A resin, which is know to be, and is commonly employed as, an effective agent for purifying molecules comprising an Fc moiety, as well as Protein G and synthetic mimetic affinity resins. Other materials that can be employed include HIC and ion exchange resins (see Example 4), depending on the properties of the protein to be purified.

It is noted that when performing the method, the refold solution comprising the refolded protein of interest is applied directly to the separation matrix, without the need for diluting or removing the components of the solution required for refolding the protein. This is an advantage of the disclosed method. Initially, it was expected that the highly ionic and/or chaotropic compounds and various other components of the refold solution would inhibit the association of the protein with the separation matrix. However, in contrast to reports in the literature (e.g., Wang et al. (1997) *Biochemical Journal.* 325(Part 3):707-710), it was surprising to observe that the protein was in fact able to associate with the separation matrix in the presence of the components of the refold solution. The unexpected finding that the protein could associate with the separation matrix in the presence of the components of the refold solution facilitates the elimination of a dilution step or buffer exchange operation, providing a savings of time and resources.

After the protein of interest has associated with the separation matrix the separation matrix is washed to remove unbound protein, lysate, impurities and unwanted components of the refold solution.

The wash buffer can be of any composition, as long as the composition and pH of the wash buffer is compatible with both the protein and the matrix. Examples of suitable wash buffers that can include, but are limited to, solutions containing glycine, tris, citrate, or phosphate. These solutions may also contain an appropriate salt. Suitable salts include, but are not limited to, sodium, potassium, ammonium, magnesium, calcium, chloride, fluoride, acetate, phosphate, and/or citrate. The pH range is chosen to optimize the chromatography conditions, preserve protein binding, and to retain the desired characteristics of the protein of interest. The resin can be washed once or any number of times. The exact composition of a wash buffer will vary with the protein being purified.

After the separation matrix with which the protein has associated has been washed, the protein of interest is eluted using an appropriate solution (e.g., a low pH buffered solution or a salt solution) to form an elution pool comprising the protein of interest.

The protein of interest can be eluted using a solution that interferes with the binding of the adsorbent component of the separation matrix to the protein, for example by disrupting the interactions between Protein A and the Fc region of a protein of interest. This solution may include an agent that can either increase or decrease pH, and/or a salt. In various embodiments, the elution solution can comprise acetic acid, glycine, or citric acid. Elution can be achieved by lowering the pH. For example, the pH can be lowered to about 4.5 or less, for example to between about 3.3 to about 4.2 (e.g., 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1 or 4.2, using a solution comprising citrate or acetate, among other possibilities.

In some situations, the protein can then be further purified from the elution pool and can be further refolded, if necessary. In other situations the protein need not be further purified and instead can be further refolded directly in the elution pool, if necessary.

Protocols for such affinity chromatography are known in the art. See, e.g., Miller and Stone (1978), *J. Immunol. Methods* 24(1-2): 111-125. In the cases that utilize ion exchange, mixed-mode, or hydrophobic interaction chromatography, the concentration of salt can be increased or decreased to disrupt ionic interaction between bound protein and a separation matrix. Solutions appropriate to effect such elutions can include, but are not limited to, sodium, potassium, ammonium, magnesium, calcium, chloride, fluoride, acetate, phosphate, and/or citrate. Other methods of elution are also known. Conditions for binding and eluting can be readily optimized by those skilled in the art.

The exact composition of an elution buffer will vary with the protein being purified and the separation matrix being employed.

In some cases it will be desirable to situate the separation matrix in a column format. In such cases a column can be prepared and then equilibrated before the cell suspension is loaded. Techniques for generating a chromatography column are well known and can be employed. The optional preparation and equilibration step can comprise washing the column with a buffer having an appropriate pH and composition that will prepare the media to bind a protein of interest. This step has the benefit of removing impurities present in the separation matrix and can enhance the binding of the protein to be isolated to the adsorbent component of a separation matrix.

It is noted that any or all steps of the invention can be carried out by any mechanical means. As noted, the separation matrix can be disposed in a column. The column can be run with or without pressure and from top to bottom or bottom to top. The direction of the flow of fluid in the column can be reversed during the purification process. Purifications can also be carried out using a batch process in which the solid support is separated from the liquid used to load, wash, and elute the sample by any suitable means, including gravity, centrifugation, or filtration. Moreover, purifications can also be carried out by contacting the sample with a filter that adsorbs or retains some molecules in the sample more strongly than others.

If desired, the protein concentration of a sample at any given step of the disclosed method can be determined by any suitable method. Such methods are well known in the art and include: 1) colorimetric methods such as the Lowry assay, the Bradford assay, the Smith assay, and the colloidal gold assay; 2) methods utilizing the UV absorption properties of proteins; and 3) visual estimation based on stained protein bands on gels relying on comparison with protein standards of known quantity on the same gel. See, e.g., Stoschek (1990), "Quantitation of Protein," in "Guide to Protein Purification," *Methods in Enzymology* 182: 50-68. Periodic determinations of protein concentration can be useful for monitoring the progress of the method as it is performed.

It is noted that any or all steps of the disclosed methods can be carried out manually or by any convenient automated means, such as by employing automated or computer-controlled systems.

IV. COLUMN CLEANING

In another aspect the present disclosure relates to the observation that in many cases the separation matrix employed in the methods provided herein can be cleaned after multiple separations and reused. This unexpected property of the method provides a significant cost and resource savings, particularly on the manufacturing scale, since the separation matrix need not be discarded after a separation is complete.

Common wisdom in the industry suggests that after a separation matrix, such as Protein A, is repeatedly exposed to highly heterogenous feedstocks comprising high lipid and host protein content it becomes irreversibly contaminated and unusable when treated with the mild regeneration solutions commonly utilized for protein-based affinity resins. The disclosed methods, however, avoid this situation and extend the usable lifetime of a separation matrix. In the context of a large scale manufacturing process this can translate into a measurable savings of time and money. Moreover, the cleaning step can be performed, as disclosed in the Examples, in-place and with no need to extract the separation matrix from a column or other matrix retaining device for cleaning, thus saving time and resources.

In one embodiment of a cleaning operation of a separation matrix, following a separation employing the disclosed method the separation matrix is washed with a regeneration reagent, such as sodium hydroxide, or an acidic reagent, such as phosphoric acid.

In one particular embodiment of a cleaning operation, Protein A is the separation matrix and a column containing Protein A resin is washed with 5 column volumes of 150 mM phosphoric acid and held for >15 minutes over the column. Following the wash with the acid, the column can be flushed with water, regenerated with 5 column volumes of 50 mM Tris, 10 mM citrate, 6M urea, 50 mM DTT; pH 7.4, subsequently washed with water, and then flushed with 3 column volumes of 150 mM phosphoric acid. This cleaning protocol has been utilized to achieve over 200 cycles of protein A resin. FIG. **3** highlights the results achievable using the disclosed cleaning methods.

EXAMPLES

The following examples demonstrate embodiments and aspects of the present invention and are not intended to be limiting.

Example 1

Direct Capture of Proteins Expressed in a Soluble Form Using Protein A Affinity Chromatography

The following experiment demonstrates that a protein comprising a plurality of polypeptides joined to an Fc moiety can be separated from an *E. coli* cell lysate slurry using a Protein A affinity media.

A protein comprising a plurality of polypeptides joined to an Fc moiety was expressed in an *E. coli* fermentation induced at 30° C. and driven to express soluble-form protein product. The fermentation broth was centrifuged, the liquid fraction removed, and the cell paste was collected. The cells were resuspended in a 10 mM potassium phosphate, 5 mM EDTA; pH 6.8 buffer solution, to approximately 100% of the original volume. The cells were then lysed by means of three passes through a high pressure homogenizer. After the cells were lysed, the cell lysate was filtered through a 0.1 μm filter to reduce particulate levels. The material was then stored in a closed bottle for ~24 hours at approximately 5° C.

In a separate operation, a packed column comprising GE Healthcare Mab Select™ Protein A affinity resin was prepared and equilibrated with 5 column volumes (CV) of 10 mM Tris; pH 8.0.

An aliquot of a protein comprising an Fc moiety was sampled directly from a lysate. The protein mixture was loaded to approximately 0.02 millimoles total protein/L resin at a 6-10 minute residence time. See FIG. **1**, which correlates protein bound and protein loaded as a function of residence time.

After loading, the column was washed with 10 mM Tris; pH 8.0, for 5 CV at up to 220 cm/hr. The protein of interest was recovered from the resin by elution with 50 mM sodium acetate, pH 3.1 at up to 220 cm/hr. The elution pool yielded greater than 90% recovery of the soluble material in the initial cell broth. The collected protein in the elution pool was stored at 2-8° C. until the next purification step was carried out.

Following the separation, the resin media was cleaned in-place by flowing 5 CV of 6 M Guanidine, pH 8.0 at 220 cm/hr.

The results of this separation demonstrated that a soluble protein expressed in a non-mammalian system can be captured and purified, with high yield, directly from cell lysate broth without having to refold the protein prior to application to a separation matrix.

Example 2

Capture of a Fc-Containing Protein Expressed in a Limited Solubility Form from a Refold Mixture Using Protein A Affinity Chromatography

The following experiments demonstrate that an Fc-containing protein can be separated from a refold mixture comprising glycerol, guanidine, urea, and arginine using Protein A affinity media.

In one experiment, a recombinant protein comprising a biologically active peptide linked to the C-terminus of the Fc moiety of an IgG1 molecule via a linker and having a molecular weight of about 57 kDa and comprising 8 disulfide bonds, in a non-mammalian expression system, namely *E. coli*, harvested, refolded under appropriate conditions, and captured using Protein A affinity media.

The growth media in which the cells were growing was centrifuged and the liquid fraction removed, leaving the cells as a paste. The cells were resuspended in water to approximately 60% of the original volume. The cells were lysed by means of three passes through a high pressure homogenizer.

After the cells were lysed, the lysate was centrifuged in a disc-stack centrifuge to collect the protein in the solid fraction, which was expressed in a limited solubility non-native form, namely as inclusion bodies.

The protein slurry was washed multiple times by resuspending the slurry in water to between 50 and 80% of the original fermentation broth volume, mixing, and centrifugation to collect the protein in the solid fraction.

The concentrated protein was then combined in a solubilization solution containing the protein, guanidine, urea, and DTT.

After incubation for one hour, the protein solution was diluted in to a refold buffer containing appropriate levels of arginine, urea, glycerol, cysteine, and cystamine.

In a separate operation, a packed column comprising ProSep VA Ultra™ Protein A affinity resin with dimensions of 1.1 cm internal diameter and ~25 cm height, was prepared and equilibrated with 5 column volumes (CV) of 25 mM Tris, 100 mM sodium chloride; pH 7.4, or similar buffered solution.

An aliquot of a protein comprising an Fc moiety from the refold solution was filtered through a series of depth and/or membrane filter to remove particulates. The conditioned and filtered protein mixture was loaded to approximately 0.35 millimoles total protein/L resin at a 6-10 minute residence time. See FIG. **1**, which correlates protein bound and protein loaded as a function of residence time.

After loading, the column was washed with 25 mM Tris, 100 mM sodium chloride; pH 7.4, or similar buffered solution, for 4.5 CV at up to 400 cm/hr. The Fc-containing protein was recovered from the resin by elution with 100 mM sodium acetate, pH 3.7 at up to 300 cm/hr. The average level of purity achieved is shown in FIG. **3**.

Following the separation, the resin media was cleaned in-place by flowing 5 CV of 150 mM phosphoric acid. The column was regenerated with 5CV of 50 mM Tris, 10 mM citrate, 6M urea and 50 mM DTT; pH 7.4, washed with water, and then flushed with 3CV of 150 mM phosphoric acid.

The results of this separation demonstrate that an insoluble protein expressed in a non-mammalian system can be purified directly from a refold buffer without having to dilute the refold buffer prior to application to a separation matrix for more than 150 cycles, as indicated by the table presented in FIG. **3**.

In another separation, the Protein A column was cycled with the above procedure 8-10 times and then the final cycle was run as follows: The media was equilibrated with 5 column volumes (CV) of 25 mM Tris, 100 mM sodium chloride; pH 7.4, or similar buffered solution. An aliquot of protein sampled directly from a refold buffer was filtered through a series of depth and/or membrane filter to remove particulates. The conditioned and filtered protein mixture was then loaded on the column to 0.35 millimoles total protein/L resin at a 6-10 minute residence time. See FIG. **1**, which correlates protein bound and protein loaded as a function of residence time.

After loading, the column was washed with 25 mM Tris, 100 mM sodium chloride; pH 7.4, or similar buffered solution, for 4.5 CV at up to 400 cm/hr. The protein of interest was recovered from the resin by eluting with 100 mM sodium acetate, pH 3.7 at up to 300 cm/hr. The resin media was cleaned in-place by flowing 5 CV of 150 mM phosphoric acid over it. Finally, the column was flushed with water, regenerated with 5CV of 50 mM Tris, 10 mM citrate, 6M urea, and 50 mM DTT; pH 7.4, washed with water, and then flushed with 3CV of 150 mM phosphoric acid. Subsequent analysis of the resin showed no protein carry-over between cycles, demonstrating the ability to reuse the resin after both cleaning methods.

Example 3

Separation of an Fc-Containing Protein from a Refold Mixture Using Cation Exchange Chromatography

The following experiments demonstrate that an Fc-containing protein can be separated from a refold mixture comprising glycerol, guanidine, urea, and arginine using cation exchange media.

In one experiment, a recombinant protein comprising a biologically active peptide linked to the C-terminus of the Fc moiety of an IgG1 molecule via a linker and having a molecular weight of about 57 kDa and comprising 8 disulfide bonds, was expressed in a non-mammalian expression system, namely *E. coli*, harvested, refolded under appropriate conditions, and captured using cation exchange media.

The growth media in which the cells were growing was centrifuged and the liquid fraction removed, leaving the cells as a paste. The cells were resuspended in water. The cells were lysed by means of multiple passes through a high pressure homogenizer. After the cells were lysed, the lysate was centrifuged to collect the protein, which was expressed in a limited solubility non-native form, namely as inclusion bodies. The protein slurry was washed multiple times by resuspending the slurry in water, mixing, and centrifugation to collect the protein. The concentrated protein was then transferred to a solubilization buffer containing guanidine and DTT. After incubation for one hour, the protein solution was diluted in to a refold buffer containing appropriate levels of arginine, urea, glycerol, cysteine, and cystamine.

In a separate operation, a packed column comprising EMD Fractogel SO_3^- cation exchange resin with dimensions of 1.1 cm internal diameter and 20 cm height, was prepared and equilibrated with 5 column volumes of 30 mM MES; pH 4.5 buffered solution.

An aliquot of a protein comprising an Fc moiety was sampled directly from a refold solution, was diluted 3-fold with water, titrated with 50% hydrochloric acid to ~pH 4.5 and was filtered through a series of depth and/or membrane filter to remove particulates. The conditioned and filtered protein mixture was loaded to approximately 0.96 millimoles total protein/L resin at 60 cm/hr.

After loading, the column was washed with 30 mM MES; pH 4.5, for 3 CV at 60 cm/hr, then washed with an additional 3 CV of 30 mM MES; pH 6.0. The protein of interest was recovered from the resin by gradient elution over 25 CV between 30 mM MES; pH 6.0 and 30 mM MES, 500 mM

NaCl; pH 6.0 at 60 cm/hr. The collected protein in the elution pool was stored at 2-8° C. until the next purification step was carried out.

Purity levels achieved, as determined by SEC and RP-HPLC are shown in FIG. **5**.

Following the separation, the resin media was cleaned in-place by flowing 3 CV of 1 M sodium hydroxide, at 120 cm/hr and held for 60 minutes prior an additional 3CV wash with 1 m sodium hydroxide.

The results of this separation demonstrate that an insoluble protein expressed in a non-mammalian system can be captured and purified from a refold buffer with a variety of separation matrices, including an ion-exchange separation matrix.

Example 4

Re-Usability of Protein A Affinity Resin Used to Isolate a Fc-Containing Protein Directly from a Refold Buffer by Affinity Chromatography

In another aspect of the method, a range of column cleaning methods can be employed in conjunction with the methods described herein, allowing the chromatography resins to be reused to an extent that make the method economically feasible. As described in Examples 2 and 3 for the case of Protein A affinity resins, cleaning protocols have been developed and demonstrated to remove product and non-product contaminants from the resin to allow reuse. The cleaning agents include caustic (e.g. sodium or potassium hydroxide), detergents (e.g. SDS or Triton X-100), denaturants (e.g. urea or guanidine-derivatives), and reductants (e.g. DTT, or thioglycolates). These agents can be used in combination or alone.

In order to demonstrate the reusability of column resins following application of the direct capture methods described, an aliquot of pH adjusted and filtered Fc-containing protein was loaded on new, unused resin and resin that had been previously cycled 94 times to evaluate the cleaning of the Protein A resin and the effect on purification binding and separation of an Fc-containing protein with regard to resin history.

The media was equilibrated with 5 column volumes (CV) of 25 mM Tris, 100 mM sodium chloride; pH 7.4, or similar buffered solution. An aliquot of protein sampled directly from a refold buffer was filtered through a series of depth and/or membrane filter to remove particulates. The conditioned and filtered protein mixture was then loaded on the column to approximately 0.35 millimoles total protein/mL resin at a 6-10 minute residence time. See FIG. **1**, which correlates protein bound and protein loaded as a function of residence time.

After loading, the column was washed with 25 mM Tris, 100 mM sodium chloride; pH 7.4, or similar buffered solution, for 4.5 CV at up to 400 cm/hr. The protein of interest was recovered from the resin by eluting with 100 mM sodium acetate, pH 3.7 at up to 300 cm/hr. Each column was regenerated using 5CV phosphoric acid and 5 CV of an acidic buffered solution containing 50 mM Tris, 10 mM citrate, 6M urea, and 50 mM DTT; pH 7.4.

This procedure was repeated for greater than 100 cycles. Selected samples from this reuse study were submitted for SEC-HPLC analysis. The goal was to track the % MP purity, % HMW and % dimer species from the pools as well as to understand the change of purity level from the load. No major differences were observed between the used columns and new columns.

This Example demonstrates that not only can a complex protein be captured from a complex chemical solution, but that the resin can be cycled repeatedly and cleaned and reused reproducibly over a number of industrially-relevant cycles.

What is claimed is:

1. A method of purifying a protein expressed in a non-native soluble form in a non-mammalian expression system comprising:

(a) lysing a non-mammalian cell in which the protein is expressed in a nonnative soluble form to generate a cell lysate;

(b) contacting the cell lysate with a separation matrix under conditions suitable for the protein to associate with the separation matrix;

(c) washing the separation matrix; and

(d) eluting the protein from the separation matrix.

2. The method of claim **1**, wherein the protein is a complex protein.

3. The method of claim **2**, wherein the complex protein is selected from the group consisting of a multimeric protein, an antibody and an Fc fusion protein.

4. The method of claim **1**, wherein the non-mammalian expression system comprises bacteria or yeast cells.

5. The method of claim **1**, wherein the separation matrix is an affinity resin.

6. The method of claim **1**, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

7. The method of claim **1**, wherein the cell lysate is filtered before it is contacted with the separation matrix.

8. The method of claim **1**, further comprising refolding the protein to its native form after it is eluted.

9. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:

(a) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:

(i) a denaturant;

(ii) a reductant; and

(iii) a surfactant;

(b) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:

(i) a denaturant;

(ii) an aggregation suppressor;

(iii) a protein stabilizer; and

(iv) a redox component;

(c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;

(d) washing the separation matrix; and

(e) eluting the protein from the separation matrix.

10. The method of claim **9**, wherein the non-native limited solubility form is a component of an inclusion body.

11. The method of claim **9**, wherein the protein is a complex protein.

12. The method of claim **10**, wherein the complex protein is selected from the group consisting of a multimeric protein, an antibody, a peptibody, and an Fc fusion protein.

13. The method of any one of claims **9-12**, wherein the non-mammalian expression system comprises bacteria or yeast cells.

14. The method of any one of claims **9-12**, wherein the denaturant of the solubilization solution or the refold buffer

comprises one or more of urea, guanidinium salts, dimethyl urea, methylurea and ethylurea.

15. The method of claim **9**, wherein the reductant comprises one or more of cysteine, dithiothreitol (DTT), beta-mercaptoethanol and glutathione.

16. The method of claim **9**, wherein the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate.

17. The method of claim **9**, wherein the aggregation suppressor is selected from the group consisting of arginine, proline, polyethylene glycols, nonionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes.

18. The method of claim **9**, wherein the protein stabilizer comprises one or more of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, tris, sodium sulfate, potassium sulfate and osmolytes.

19. The method of claim **9**, wherein the redox component comprises one or more of glutathione-reduced, glutathione-oxidized, cysteine, cystine, cysteamine, cystamine and beta-mercaptoethanol.

20. The method of claim **9**, wherein the separation matrix is:

(i) an affinity resin, selected from the group consisting of Protein A, Protein G, and synthetic mimetic affinity resin; or

(ii) a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

21. The method of any one of claim **1** or **9-12**, wherein the protein is isolated after elution from the separation matrix.

22. The method of claim **8**, wherein the protein is isolated after refolding.

23. The method of claim **14**, wherein the reductant comprises one or more of cysteine, dithiothreitol (DTT), beta-mercaptoethanol and glutathione.

24. The method of claim **15**, wherein the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate.

25. The method of claim **16**, wherein the aggregation suppressor is selected from the group consisting of arginine, proline, polyethylene glycols, nonionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes.

26. The method of claim **17**, wherein the protein stabilizer comprises one or more of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, tris, sodium sulfate, potassium sulfate and osmolytes.

27. The method of claim **18**, wherein the redox component comprises one or more of glutathione-reduced, glutathione-oxidized, cysteine, cystine, cysteamine, cystamine and beta-mercaptoethanol.

28. The method of claim **19**, wherein the separation matrix is:

(i) an affinity resin, selected from the group consisting of Protein A, Protein G, and synthetic mimetic affinity resin; or

(ii) a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

29. The method of claim **13**, wherein the protein is isolated after elution from the separation matrix.

30. The method of claim **20**, wherein the protein is isolated after elution from the separation matrix.

* * * * *

EXHIBIT 2

U.S. FDA APPROVES PFIZER'S BIOSIMILAR NIVESTYM™ (FILGRASTIM-AAFI)

NIVESTYM™, A BIOSIMILAR TO NEUPOGEN ® (FILGRASTIM), IS PFIZER'S FOURTH BIOSIMILAR TO BE APPROVED BY THE FDA

Friday, July 20, 2018 - 4:24pm EDT

Pfizer Inc. (NYSE:PFE) today announced that the United States (U.S.) Food and Drug Administration (FDA) has approved NIVESTYM™ (filgrastim-aafi), a biosimilar to Neupogen[1] (filgrastim), for all eligible indications of the reference product.

"The FDA approval of NIVESTYM marks an important step in helping expand access to critical treatment options for patients with neutropenia, many of whom have cancer and can be hospitalized for potentially life-threatening side effects stemming from chemotherapy," said Berk Gurdogan, U.S. Institutions President, Pfizer Essential Health. "We believe biosimilars, like NIVESTYM, are essential in helping to address evolving healthcare needs and may provide more affordable medicines to patients."

The FDA approval was based on a review of a comprehensive data package and totality of evidence demonstrating a high degree of similarity of NIVESTYM compared to its reference product.

In the U.S., NIVESTYM is indicated:[2]

- To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- For reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- To reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
- For the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
- For chronic administration to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

NIVESTYM is expected to be available in the U.S. at a significant discount to the current wholesale acquisition cost (WAC) of Neupogen. WAC is not inclusive of discounts to payers, providers, distributors and other purchasing organizations.

NIVESTYM is Pfizer's fourth biosimilar to be approved by the U.S. FDA. Pfizer's biosimilars pipeline consists of 10 distinct biosimilar molecules with five assets in mid-to-late stage clinical development.[3]

NIVESTYM™ IMPORTANT SAFETY INFORMATION

Do not take NIVESTYM if you have had a serious allergic reaction to human G-CSFs such as filgrastim or pegfilgrastim products.

Before you take NIVESTYM, tell your healthcare provider all about your medical conditions, including if you:

- have a sickle cell disorder
- have kidney problems
- are receiving radiation therapy
- are pregnant or plan to become pregnant. It is not known if NIVESTYMwill harm your unborn baby
- are breastfeeding or plan to breastfeed. It is not known if NIVESTYMpasses into your breast milk

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive NIVESTYM?

- NIVESTYMinjections can be given by a healthcare provider by intravenous (IV) infusion or under your skin (subcutaneous injection). Your healthcare provider may decide that subcutaneous injections can be given at home by you or your caregiver. If NIVESTYMis given at home, see the detailed "Instructions for Use" that comes with your NIVESTYMprescription for information on how to prepare and inject a dose of NIVESTYM.
- You and your caregiver should be shown how to prepare and inject NIVESTYM, before you use it, by your healthcare provider.
- Your healthcare provider will tell you how much NIVESTYMto inject and when to inject it. Do not change your dose or stop NIVESTYMunless your healthcare provider tells you to.
- If you are receiving NIVESTYMbecause you are also receiving chemotherapy, your dose of NIVESTYMshould be injected at least 24 hours before or 24 hours after your dose of chemotherapy.
- If you miss a dose of NIVESTYM, talk to your healthcare provider about when you should give your next dose.

What are the most common side effects of NIVESTYM?

- The most common side effects of NIVESTYM include aching in the bones and muscles.

What are possible side effects of NIVESTYM?

NIVESTYM may cause serious side effects including:

- **Spleen rupture.** Your spleen may become enlarged and can rupture. A ruptured spleen can cause death.
- **Acute Respiratory Distress Syndrome (ARDS).** ARDS is a serious lung problem.
- **Serious allergic reactions.** These can occur anywhere in your body. If you have an allergic reaction, stop using NIVESTYM.

- **Sickle cell crises.** Serious sickle cell crises have happened in people with sickle cell disorders receiving NIVESTYM that have sometimes led to death.
- **Kidney injury (glomerulonephritis).** NIVESTYM can cause kidney injury.
- **Capillary Leak Syndrome.** NIVESTYM can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening.
- **Decreased platelet count (thrombocytopenia).** Your healthcare provider will check your blood during treatment with NIVESTYM. Tell your healthcare provider if you have unusual bleeding or bruising during treatment with NIVESTYM. This could be a sign of decreased platelet counts, which may reduce the ability of your blood to clot.
- **Increased white blood cell count (leukocytosis).** Your healthcare provider will check your blood during treatment with NIVESTYM.
- **Inflammation of your blood vessels (cutaneous vasculitis).** Tell your healthcare provider if you develop purple spots or redness of your skin.

Call your healthcare provider or seek emergency medical help right away if you have:

- pain in the left upper stomach area or left shoulder
- symptoms of sickle cell crisis such as pain or trouble breathing
- shortness of breath, with or without a fever, any trouble breathing, wheezing or a fast rate of breathing
- a rash over your whole body, swelling around your mouth or eyes, fast heart rate and sweating
- swelling or puffiness, especially swelling of your stomach-area and feeling of fullness
- swelling of your face and ankles
- blood in your urine or dark colored urine
- less than usual urination
- dizziness or are feeling faint
- a general feeling of tiredness

These are not all the possible side effects of NIVESTYM. Call your healthcare provider for medical advice about side effects.

You are encouraged to report adverse events related to Pfizer products by calling 1-800-438-1985 (U.S. only). If you prefer, you may contact the U.S. Food and Drug Administration (FDA) directly. Visit http://www.fda.gov/MedWatch or call 1-800-FDA-1088.

Please see full Prescribing Information and Patient Information for NIVESTYM (filgrastim-aafi).

Working together for a healthier world®

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent

with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News , LinkedIn , YouTube and like us on Facebook at Facebook.com/Pfizer .

DISCLOSURE NOTICE: The information contained in this release is as of July 20, 2018. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about NIVESTYM™ (filgrastim-aafi), including its potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the launch timing and commercial success of NIVESTYM in the United States; the uncertainties inherent in research and development; whether and when any applications for NIVESTYM may be filed with regulatory authorities in any other jurisdictions; whether and when regulatory authorities in any other jurisdictions may approve any such other applications that are pending or that may be filed for NIVESTYM, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted and, if approved, whether NIVESTYM will be commercially successful; intellectual property and/or litigation implications; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of NIVESTYM; uncertainties regarding access challenges for our biosimilar products where our product may not receive access at parity to the innovator product and remains in a disadvantaged position; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2017, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 10-Q and Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

[1] Neupogen® is a registered trademark of Amgen Inc.

[2] Nivestym™ (filgrastim-aafi) Prescribing Information. New York. NY: Pfizer Inc: 2018. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761080s000lbl.pdf?utm_campaign=FDA%20approves%20Nivestym%20%28filgrastim-aafi%29%20a%20biosimilar%20to%20Neupogen%20%28filgrastim%29&utm_medium=email&utm_source=Eloqua .

[3] Pfizer. (2018, January 30). Pfizer pipeline. Retrieved from https://www.pfizer.com/sites/default/files/product-pipeline/01302018_PipelineUpdate.pdf.

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EXHIBIT 3

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-Q

X QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

For the quarterly period ended September 30, 2018

OR

TRANSITION REPORT PURSUANT TO SECTION 13
OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

COMMISSION FILE NUMBER 1-3619

PFIZER INC .

(Exact name of registrant as specified in its charter)

DELAWARE	13-5315170
(State of Incorporation)	(I.R.S. Employer Identification No.)

235 East 42 nd Street, New York, New York 10017
(Address of principal executive offices) (zip code)
(212) 733-2323
(Registrant's telephone number)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

YES X NO ___

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files).

YES X NO ___

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act (check one):

Large Accelerated filer X Accelerated filer ___ Non-accelerated filer ___ Smaller reporting company ___ Emerging growth company ___

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ___

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

YES ____ NO X

At November 5, 2018 , 5,780,474,578 shares of the issuer's voting common stock were outstanding.

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GLOSSARY OF DEFINED TERMS

Unless the context requires otherwise, references to "Pfizer," "the Company," "we," "us" or "our" in this Quarterly Report on Form 10-Q (defined below) refer to Pfizer Inc. and its subsidiaries. We also have used several other terms in this Quarterly Report on Form 10-Q, most of which are explained or defined below:

2017 Financial Report	Financial Report for the fiscal year ended December 31, 2017, which was filed as Exhibit 13 to the Annual Report on Form 10-K for the fiscal year ended December 31, 2017
2017 Form 10-K	Annual Report on Form 10-K for the fiscal year ended December 31, 2017
ACA (Also referred to as U.S. Healthcare Legislation)	U.S. Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act
ACIP	Advisory Committee on Immunization Practices
ALK	anaplastic lymphoma kinase
Alliance revenues	Revenues from alliance agreements under which we co-promote products discovered or developed by other companies or us
Allogene	Allogene Therapeutics, Inc.
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Anacor	Anacor Pharmaceuticals, Inc.
AOCI	Accumulated Other Comprehensive Income
Astellas	Astellas Pharma Inc., Astellas US LLC and Astellas Pharma US, Inc.
ASU	Accounting Standards Update
ATM-AVI	aztreonam-avibactam
Avillion	Avillion LLP
Bain Capital	Bain Capital Private Equity and Bain Capital Life Sciences
Biogen	Biogen Inc.
BMS	Bristol-Myers Squibb Company
BRCA	BReast CAncer susceptibility gene
CAR T	chimeric antigen receptor T cell
CDC	U.S. Centers for Disease Control and Prevention
Cellectis	Cellectis S.A.
Cerevel	Cerevel Therapeutics, LLC
CIAS	cognitive impairment associated with schizophrenia
Citibank	Citibank, N.A.
CML	chronic myelogenous leukemia
Developed Markets	U.S., Western Europe, Japan, Canada, Australia, South Korea, Scandinavian countries, Finland and New Zealand
EEA	European Economic Area
EH	Essential Health
EMA	European Medicines Agency
Emerging Markets	Includes, but is not limited to, the following markets: Asia (excluding Japan and South Korea), Latin America, Eastern Europe, Africa, the Middle East, Central Europe and Turkey
EPS	earnings per share
EU	European Union
Exchange Act	Securities Exchange Act of 1934, as amended
FASB	Financial Accounting Standards Board
FDA	U.S. Food and Drug Administration
GAAP	Generally Accepted Accounting Principles
GIST	gastrointestinal stromal tumors
GPD	Global Product Development
HER2-	human epidermal growth factor receptor 2-negative
hGH-CTP	human growth hormone
HIS	Hospira Infusion Systems
Hisun Pfizer	Hisun Pfizer Pharmaceuticals Company Limited
Hospira	Hospira, Inc.
HR+	hormone receptor-positive
ICU Medical	ICU Medical, Inc.
IH	Innovative Health
IPR&D	in-process research and development
IRS	U.S. Internal Revenue Service

IV	intravenous
Janssen	Janssen Biotech Inc.
J&J	Johnson & Johnson
King	King Pharmaceuticals LLC (formerly King Pharmaceuticals, Inc.)
LDL	low density lipoprotein
LEP	Legacy Established Products
LIBOR	London Interbank Offered Rate
Lilly	Eli Lilly & Company
LOE	loss of exclusivity
MCC	Merkel Cell Carcinoma
MCO	Managed Care Organization
MD&A	Management's Discussion and Analysis of Financial Condition and Results of Operations
Medivation	Medivation LLC (formerly Medivation, Inc.)
Merck	Merck & Co., Inc.
Meridian	Meridian Medical Technologies, Inc.
Moody's	Moody's Investors Service
NDA	new drug application
NovaQuest	NovaQuest Co-Investment Fund V, L.P.
NSCLC	non-small cell lung cancer
NYSE	New York Stock Exchange
OPKO	OPKO Health, Inc.
OTC	over-the-counter
PARP	poly ADP ribose polymerase
PBM	Pharmacy Benefit Manager
Pharmacia	Pharmacia Corporation
PP&E	Property, plant & equipment
Quarterly Report on Form 10-Q	Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2018
RCC	renal cell carcinoma
R&D	research and development
RPI	RPI Finance Trust
Sandoz	Sandoz, Inc., a division of Novartis AG
SEC	U.S. Securities and Exchange Commission
Servier	Les Laboratoires Servier SAS
SFJ	SFJ Pharmaceuticals Group
Shire	Shire International GmbH
SI&A	Selling, informational and administrative
SIP	Sterile Injectable Pharmaceuticals
S&P	Standard and Poor's
StratCO	Strategy and Commercial Operations
Tax Cuts and Jobs Act or TCJA	Legislation commonly referred to as the U.S. Tax Cuts and Jobs Act of 2017
Teuto	Laboratório Teuto Brasileiro S.A.
U.K.	United Kingdom
U.S.	United States
ViiV	ViiV Healthcare Limited
WRD	Worldwide Research and Development

PART I - FINANCIAL INFORMATION
Item 1. Financial Statements

PFIZER INC. AND SUBSIDIARY COMPANIES
CONDENSED CONSOLIDATED STATEMENTS OF INCOME
(UNAUDITED)

	Three Months Ended		Nine Months Ended	
(MILLIONS, EXCEPT PER COMMON SHARE DATA)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Revenues	$ 13,298	$ 13,168	$ 39,670	$ 38,843
Costs and expenses:				
Cost of sales [a]	2,694	2,844	8,173	7,972
Selling, informational and administrative expenses [a]	3,494	3,504	10,448	10,249
Research and development expenses [a]	2,008	1,865	5,549	5,367
Amortization of intangible assets	1,253	1,177	3,640	3,571
Restructuring charges and certain acquisition-related costs	85	114	172	267
Other (income)/deductions—net	(414)	79	(1,143)	65
Income from continuing operations before provision for taxes on income	4,177	3,585	12,831	11,351
Provision for taxes on income	66	727	1,270	2,287
Income from continuing operations	4,111	2,858	11,562	9,064
Discontinued operations—net of tax	11	—	10	1
Net income before allocation to noncontrolling interests	4,122	2,858	11,571	9,066
Less: Net income attributable to noncontrolling interests	8	18	25	32
Net income attributable to Pfizer Inc.	$ 4,114	$ 2,840	$ 11,546	$ 9,034
Earnings per common share—basic :				
Income from continuing operations attributable to Pfizer Inc. common shareholders	$ 0.70	$ 0.48	$ 1.96	$ 1.51
Discontinued operations—net of tax	—	—	—	—
Net income attributable to Pfizer Inc. common shareholders	$ 0.70	$ 0.48	$ 1.96	$ 1.51
Earnings per common share—diluted :				
Income from continuing operations attributable to Pfizer Inc. common shareholders	$ 0.69	$ 0.47	$ 1.92	$ 1.49
Discontinued operations—net of tax	—	—	—	—
Net income attributable to Pfizer Inc. common shareholders	$ 0.69	$ 0.47	$ 1.92	$ 1.49
Weighted-average shares—basic	5,875	5,951	5,899	5,972
Weighted-average shares—diluted	5,986	6,041	5,998	6,057
Cash dividends paid per common share	$ 0.34	$ 0.32	$ 1.02	$ 0.96

[a] Excludes amortization of intangible assets, except as disclosed in *Note 9A. Identifiable Intangible Assets and Goodwill: Identifiable Intangible Assets.*
Amounts may not add due to rounding.

See Notes to Condensed Consolidated Financial Statements.

PFIZER INC. AND SUBSIDIARY COMPANIES
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME
(UNAUDITED)

(MILLIONS OF DOLLARS)	Three Months Ended		Nine Months Ended	
	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Net income before allocation to noncontrolling interests	$ 4,122	$ 2,858	$ 11,571	$ 9,066
Foreign currency translation adjustments, net	(567)	878	(507)	1,352
Reclassification adjustments	(2)	(3)	(22)	110
	(569)	875	(530)	1,461
Unrealized holding gains/(losses) on derivative financial instruments, net	222	(50)	236	(149)
Reclassification adjustments for (gains)/losses included in net income [a]	(235)	56	119	(393)
	(13)	6	355	(542)
Unrealized holding gains/(losses) on available-for-sale securities, net	149	384	(65)	698
Reclassification adjustments for gains included in net income [a]	(36)	(278)	(67)	(181)
Reclassification adjustments for unrealized gains included in *Retained earnings* [b]	—	—	(462)	—
	112	106	(595)	518
Benefit plans: actuarial gains/(losses), net	8	(103)	114	(41)
Reclassification adjustments related to amortization	60	140	183	448
Reclassification adjustments related to settlements, net	42	38	108	89
Other	49	(76)	69	(111)
	158	(1)	474	384
Benefit plans: prior service costs and other, net	—	—	—	(2)
Reclassification adjustments related to amortization	(46)	(46)	(137)	(138)
Reclassification adjustments related to curtailments, net	(4)	(3)	(18)	(14)
Other	—	1	1	2
	(50)	(48)	(154)	(151)
Other comprehensive income/(loss), before tax	(361)	938	(449)	1,669
Tax provision/(benefit) on other comprehensive income/(loss)	62	(80)	667	(218)
Other comprehensive income/(loss) before allocation to noncontrolling interests	$ (422)	$ 1,018	$ (1,116)	$ 1,888
Comprehensive income before allocation to noncontrolling interests	$ 3,700	$ 3,876	$ 10,455	$ 10,953
Less: Comprehensive income attributable to noncontrolling interests	—	19	5	48
Comprehensive income attributable to Pfizer Inc.	$ 3,700	$ 3,857	$ 10,450	$ 10,906

[a] Reclassified into *Other (income)/deductions—net* and *Cost of sales* in the condensed consolidated statements of income. For additional information on amounts reclassified into *Cost of sales,* see *Note 7F. Financial Instruments: Derivative Financial Instruments and Hedging Activities.*

[b] For additional information, see *Note 1B . Basis of Presentation and Significant Accounting Policies: Adoption of New Accounting Standards .*

Amounts may not add due to rounding.

See Notes to Condensed Consolidated Financial Statements.

PFIZER INC. AND SUBSIDIARY COMPANIES
CONDENSED CONSOLIDATED BALANCE SHEETS

(MILLIONS OF DOLLARS)	September 30, 2018	December 31, 2017
	(Unaudited)	
Assets		
Cash and cash equivalents	$ 3,559	$ 1,342
Short-term investments	13,680	18,650
Trade accounts receivable, less allowance for doubtful accounts: 2018—$567; 2017—$584	10,024	8,221
Inventories	8,184	7,578
Current tax assets	3,686	3,050
Other current assets	2,450	2,301
Total current assets	41,583	41,141
Long-term investments	6,444	7,015
Property, plant and equipment, less accumulated depreciation: 2018—$17,078; 2017—$16,172	14,036	13,865
Identifiable intangible assets, less accumulated amortization	45,306	48,741
Goodwill	55,614	55,952
Noncurrent deferred tax assets and other noncurrent tax assets	1,875	1,855
Other noncurrent assets	2,980	3,227
Total assets	$ 167,838	$ 171,797
Liabilities and Equity		
Short-term borrowings, including current portion of long-term debt: 2018—$4,255; 2017—$3,546	$ 7,385	$ 9,953
Trade accounts payable	4,297	4,656
Dividends payable	1,963	2,029
Income taxes payable	2,781	477
Accrued compensation and related items	2,096	2,196
Other current liabilities	10,490	11,115
Total current liabilities	29,013	30,427
Long-term debt	33,652	33,538
Pension benefit obligations, net	4,886	5,926
Postretirement benefit obligations, net	1,455	1,504
Noncurrent deferred tax liabilities	5,512	3,900
Other taxes payable	15,289	18,697
Other noncurrent liabilities	6,367	6,149
Total liabilities	96,174	100,141
Commitments and Contingencies		
Preferred stock	20	21
Common stock	466	464
Additional paid-in capital	85,828	84,278
Treasury stock	(96,574)	(89,425)
Retained earnings	91,995	85,291
Accumulated other comprehensive loss	(10,417)	(9,321)
Total Pfizer Inc. shareholders' equity	71,319	71,308
Equity attributable to noncontrolling interests	346	348
Total equity	71,664	71,656
Total liabilities and equity	$ 167,838	$ 171,797

Amounts may not add due to rounding.

See Notes to Condensed Consolidated Financial Statements.

PFIZER INC. AND SUBSIDIARY COMPANIES
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS (UNAUDITED)

(MILLIONS OF DOLLARS)	Nine Months Ended September 30, 2018	Nine Months Ended October 1, 2017
Operating Activities		
Net income before allocation to noncontrolling interests	$ 11,571	$ 9,066
Adjustments to reconcile net income before allocation to noncontrolling interests to net cash provided by operating activities:		
Depreciation and amortization	4,743	4,695
Asset write-offs and impairments	88	326
Adjustments to loss on sale of HIS net assets	(1)	52
TCJA impact [a]	(410)	—
Deferred taxes from continuing operations	(974)	241
Share-based compensation expense	682	595
Benefit plan contributions in excess of income — 2018 and expense — 2017	(1,000)	(1,042)
Other adjustments, net	(1,169)	(604)
Other changes in assets and liabilities, net of acquisitions and divestitures	(2,441)	(3,616)
Net cash provided by operating activities	11,089	9,713
Investing Activities		
Purchases of property, plant and equipment	(1,357)	(1,256)
Purchases of short-term investments	(7,364)	(6,469)
Proceeds from redemptions/sales of short-term investments	12,752	5,778
Net proceeds from redemptions/sales of short-term investments with original maturities of three months or less	385	2,758
Purchases of long-term investments	(1,503)	(2,526)
Proceeds from redemptions/sales of long-term investments	2,174	2,403
Acquisitions of businesses, net of cash acquired	—	(1,000)
Acquisitions of intangible assets	(47)	(188)
Other investing activities, net	248	519
Net cash provided by investing activities	5,289	19
Financing Activities		
Proceeds from short-term borrowings	1,945	7,003
Principal payments on short-term borrowings	(4,239)	(7,659)
Net (payments on)/proceeds from short-term borrowings with original maturities of three months or less	(973)	566
Proceeds from issuance of long-term debt	4,974	5,273
Principal payments on long-term debt	(3,104)	(4,474)
Purchases of common stock	(7,168)	(5,000)
Cash dividends paid	(6,015)	(5,750)
Proceeds from exercise of stock options	1,099	656
Other financing activities, net	(553)	(223)
Net cash used in financing activities	(14,034)	(9,607)
Effect of exchange-rate changes on cash and cash equivalents and restricted cash and cash equivalents	(116)	67
Net increase in cash and cash equivalents and restricted cash and cash equivalents	2,227	193
Cash and cash equivalents and restricted cash and cash equivalents, beginning	1,431	2,666
Cash and cash equivalents and restricted cash and cash equivalents, end	$ 3,658	$ 2,858
Supplemental Cash Flow Information		
Non-cash transactions:		
Receipt of ICU Medical common stock [b]	$ —	$ 428
Promissory note from ICU Medical [b]	—	75
Equity investment in Cerevel Therapeutics, Inc. in exchange for Pfizer's portfolio of clinical and preclinical neuroscience assets [b]	343	—
Equity investment in Allogene received in exchange for Pfizer's allogeneic CAR T developmental program assets [b]	92	—
Cash paid (received) during the period for:		
Income taxes	$ 1,666	$ 1,424

Interest	968	1,101
Interest rate hedges	(104)	(183)

(a) As a result of the enactment of the TCJA in December 2017, Pfizer's *Provision for taxes on income* for the nine months ended September 30, 2018 was favorably impacted by approximately $410 million , primarily related to certain tax initiatives associated with the TCJA, as well as favorable adjustments to the provisional estimates of the legislation. See *Note 5A . Tax Matters : Taxes on Income from Continuing Operations.*

(b) For additional information, see *Note 2B . Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment* : *Divestitures* .

Amounts may not add due to rounding.

See Notes to Condensed Consolidated Financial Statements.

Note 1. Basis of Presentation and Significant Accounting Policies

A. Basis of Presentation

See the Glossary of Defined Terms at the beginning of this Quarterly Report on Form 10-Q for terms used throughout the condensed consolidated financial statements and related notes in this Quarterly Report on Form 10-Q.

We prepared the condensed consolidated financial statements following the requirements of the SEC for interim reporting. As permitted under those rules, certain footnotes or other financial information that are normally required by U.S. GAAP can be condensed or omitted.

The financial information included in our condensed consolidated financial statements for subsidiaries operating outside the U.S. is as of and for the three and nine months ended August 26, 2018 and August 27, 2017 . The financial information included in our condensed consolidated financial statements for U.S. subsidiaries is as of and for the three and nine months ended September 30, 2018 and October 1, 2017 .

Revenues, expenses, assets and liabilities can vary during each quarter of the year. Therefore, the results and trends in these interim financial statements may not be representative of those for the full year.

We are responsible for the unaudited financial statements included in this Quarterly Report on Form 10-Q. The interim financial statements include all normal and recurring adjustments that are considered necessary for the fair statement of our condensed consolidated balance sheets and condensed consolidated statements of income. The information included in this Quarterly Report on Form 10-Q should be read in conjunction with the consolidated financial statements and accompanying notes included in our 2017 Financial Report.

We manage our commercial operations through two distinct business segments: Pfizer Innovative Health (IH) and Pfizer Essential Health (EH). For additional information, see *Note 13* and Notes to Consolidated Financial Statements— *Note 18. Segment, Geographic and Other Revenue Information* in Pfizer's 2017 Financial Report.

Certain amounts in the condensed consolidated financial statements and associated notes may not add due to rounding. All percentages have been calculated using unrounded amounts.

In the first quarter of 2018, as of January 1, 2018, we adopted eleven new accounting standards. See *Note 1B* for further information.

Our significant business development activities include:

- On February 3, 2017, we completed the sale of our global infusion systems net assets, HIS, to ICU Medical. The operating results of HIS are included in our condensed consolidated statement of income and EH's operating results through February 2, 2017 and, therefore, our financial results, and EH's operating results, for the third quarter of 2017 do not reflect any contribution from HIS global operations, while our financial results, and EH's operating results, for the first nine months of 2017 reflect approximately one month of HIS domestic operations and approximately two months of HIS international operations. Our financial results, and EH's operating results, for 2018 do not reflect any contribution from HIS global operations.

- On December 22, 2016, which fell in the first fiscal quarter of 2017 for our international operations, we acquired the development and commercialization rights to AstraZeneca's small molecule anti-infectives business, primarily outside the U.S. Commencing from the acquisition date, our financial statements reflect the assets, liabilities, operating results and cash flows of this business, and, in accordance with our international reporting period, our financial results, EH's operating results, and cash flows for the third quarter and first nine months of 2017 reflect approximately three months and eight months, respectively, of the small molecule anti-infectives business acquired from AstraZeneca. Our financial results, EH's operating results, and cash flows for the third quarter and first nine months of 2018 reflect three months and nine months , respectively, of the small molecule anti-infectives business acquired from AstraZeneca.

For additional information, see *Note 2* and Notes to Consolidated Financial Statements— *Note 2. Acquisitions, Sale of Hospira Infusion Systems Net Assets, Research and Development and Collaborative Arrangements, Equity-Method Investments and Cost-Method Investment* in Pfizer's 2017 Financial Report.

B. Adoption of New Accounting Standards

On January 1, 2018, we adopted eleven new accounting standards. The quantitative impacts on our prior period condensed consolidated financial statements of adopting the following new standards are summarized in the tables within the section titled *Impacts to our Condensed Consolidated Financial Statements* , further below.

Revenues —We adopted a new accounting standard for revenue recognition and changed our revenue recognition policies accordingly. Generally, the previous revenue recognition standards permitted recognition when persuasive evidence of a contract existed, delivery had occurred, and the seller's price to the buyer was fixed or determinable. Under the new standard, revenue is recognized upon transfer of control of the product to our customer in an amount that reflects the consideration we expect to receive in exchange. We adopted the new accounting standard utilizing the modified retrospective method, and, therefore, no adjustments were made to amounts in our prior period financial statements. We recorded the cumulative effect of adopting the standard as an adjustment to increase the opening balance of *Retained earnings* by $584 million on a pre-tax basis ($450 million after-tax). This amount includes $500 million (pre-tax) related to the timing of recognizing *Other (income)/deductions — net* primarily for upfront and milestone payments on our collaboration arrangements ($394 million , pre-tax) and, to a lesser extent, product rights and out-licensing arrangements, and $84 million (pre-tax) related to the timing of recognizing *Revenues* and *Cost of sales* on certain product shipments. The impact of adoption did not have a material impact to our condensed consolidated statements of income for the three and nine months ended September 30, 2018 or our condensed consolidated balance sheet as of September 30, 2018 . For additional information, see *Note 1C* .

Financial Assets and Liabilities —The new accounting standard related to the recognition and measurement of financial assets and liabilities makes the following changes to prior guidance and requires:

- certain equity investments to be measured at fair value with changes in fair value now recognized in net income. However, equity investments that do not have readily determinable fair values may be measured at cost minus impairment, if any, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer;
- a qualitative assessment of equity investments without readily determinable fair values to identify impairment; and
- separate presentation of financial assets and financial liabilities by measurement category and form of financial asset on the balance sheet or in the accompanying notes to the financial statements.

We adopted the new accounting standard utilizing the modified retrospective method, and, therefore, no adjustments were made to amounts in our prior period financial statements. We recorded the cumulative effect of adopting the standard as an adjustment to increase the opening balance of *Retained earnings* by $462 million on a pre-tax basis ($419 million after-tax) related to the net impact of unrealized gains and losses primarily on available-for-sale equity securities, restricted stock and private equity securities. In the third quarter of 2018, we recorded net unrealized gains on equity securities of $8 million and in the first nine months of 2018, we recorded net unrealized gains on equity securities of $344 million , in *Other (income)/deductions—net* . For additional information, see *Note 4* and *Note 7* .

Presentation of Net Periodic Pension and Postretirement Benefit Cost —We adopted a new accounting standard that requires the net periodic pension and postretirement benefit costs other than the service costs be presented in *Other (income)/deductions—net,* and that the presentation be applied retrospectively. We adopted the presentation of the net periodic benefit costs other than service costs by reclassifying these costs from *Cost of sales* , *Selling, informational and administrative expenses* , *Research and development expenses* and *Restructuring charges and certain acquisition-related costs* to *Other (income)/deductions—net* . We elected to apply the practical expedient as it is impracticable to determine the disaggregation of the cost components for amounts capitalized within *Inventories* and property, plant and equipment and amortized in each of those periods. We have therefore reclassified the prior period net periodic benefit costs/(credits) disclosed in *Note 10* to apply the retrospective presentation for comparative periods.

As of January 1, 2018, only service costs will be included in amounts capitalized in *Inventories* or property, plant and equipment, while the other components of net periodic benefit costs will be included in *Other (income)/deductions — net* . For additional information, see *Note 4* and *Note 10* .

Income Tax Accounting —The new guidance removes the prohibition against recognizing current and deferred income taxes for an intra-entity asset transfer until the asset has been sold to a third party, unless the asset transferred is inventory. We adopted the standard utilizing the modified retrospective method, and, therefore, no adjustments were made to amounts in our prior period financial statements. We recorded the cumulative effect of adopting the standard as an adjustment to decrease the opening balance of *Retained earnings* by $189 million .

Accounting for Hedging Activities —The standard includes the following changes:

- Permits hedge accounting for risk components in hedging relationships involving nonfinancial risk and interest rate risk;
- Changes the guidance for designating fair value hedges of interest rate risk and for measuring the change in fair value of the hedged item in fair value hedges of interest rate risk;
- No longer requires the separate measurement and reporting of hedge ineffectiveness, but requires the income statement presentation of the earnings effect of the hedging instrument with the earnings effect of the hedged item;
- Permits us to exclude the portion of the change in fair value of a currency swap that is attributable to a cross-currency basis spread from the assessment of hedge effectiveness; and
- Simplifies hedge effectiveness testing.

We early adopted the new accounting standard on January 1, 2018 on a prospective basis. In the third quarter of 2018, we recorded income of $23 million and in the first nine months of 2018, we recorded income of $68 million in *Other (income)/deductions — net* , whereas this item would have been classified in interest income in prior periods. For additional information, see *Note 7F* .

Reclassification of Certain Tax Effects from AOCI —We early adopted a new accounting standard that provides guidance on the reclassification of certain tax effects from AOCI. Under the new guidance, we elected to reclassify the stranded tax amounts related to the TCJA from AOCI to *Retained earnings* . We adopted the new accounting standard utilizing the modified retrospective method, and recorded the cumulative effect of adopting the standard as an adjustment to increase the opening balance of *Retained earnings* by $495 million , primarily due to the effect of the change in the U.S. Federal corporate tax rate. The impact on other stranded tax amounts related to the application of the TCJA was not material to our condensed consolidated financial statements.

Classification of Certain Transactions in the Statement of Cash Flows —We retrospectively adopted an accounting standard that changed the presentation of certain information in the condensed consolidated statements of cash flows, including the classification of:

- debt prepayment and extinguishment costs, resulting in an increase in *Operating activities — Other adjustments, net* and a decrease in *Financing activities — Other financing activities, net* of $7 million for the nine months ended September 30, 2018 ; and
- accreted interest on the settlement of commercial paper debt instruments, resulting in a decrease in *Operating activities — Other adjustments, net* , and an increase in *Financing activities — Other financing activities, net* of $69 million for the nine months ended September 30, 2018 .

The new standard also establishes guidance on the classification of certain cash flows related to contingent consideration in a business acquisition. Cash payments made soon after a business acquisition date will be classified as *Investing activities* , while payments made thereafter will be classified as *Financing activities* . Payments made in excess of the amount of the original contingent consideration liability will be classified as *Operating activities* . The adoption of this guidance did not have a material impact to our condensed consolidated financial statements.

Presentation of Restricted Cash in the Statement of Cash Flows —We adopted, on a retrospective basis, the new accounting standard, which requires that restricted cash and restricted cash equivalents be included with *Cash and cash equivalents* when reconciling the beginning-of-period and end-of-period total amounts shown in the condensed consolidated statements of cash flows. As a result, for the nine months ended September 30, 2018 , $10 million is presented as an increase in *Cash, cash equivalents, restricted cash and restricted cash equivalents.*

Definition of a Business —We prospectively adopted the standard for determining whether business development transactions should be accounted for as acquisitions (or disposals) of assets or businesses. If substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset, the transaction will not qualify for treatment as a business. To be considered a business, a set of integrated activities and assets must include, at a minimum, an input and a substantive process that together significantly contribute to the ability to create outputs, without regard as to whether a purchaser could replace missing elements. In addition, the definition of the term “output” has been narrowed to make it consistent with the updated revenue recognition guidance. In the third quarter and first nine months of 2018, there was no impact to our condensed consolidated financial statements from the adoption of this new standard.

Derecognition of Nonfinancial Assets —We prospectively adopted the standard, which applies to the full or partial sale or transfer of nonfinancial assets, including intangible assets, real estate and inventory. The standard provides that the gain or loss is determined by the difference between the consideration received and the carrying value of the asset. In the third quarter and

first nine months of 2018, there was no impact to our condensed consolidated financial statements from the adoption of this new standard.

Accounting for Modifications of Share-Based Payment Awards —We prospectively adopted the standard, which clarifies that certain changes in the terms or conditions of a share-based payment award be accounted for as a modification. There was no impact to our condensed consolidated financial statements from the adoption of this new standard.

Impacts to our Condensed Consolidated Financial Statements —The impacts on our prior period condensed consolidated financial statements of adopting the new standards described above are summarized in the following tables:

Adoption of the standard related to pension and postretirement benefit costs impacted our prior period condensed consolidated statements of income as follows:

	Three Months Ended October 1, 2017		
(MILLIONS OF DOLLARS)	As Previously Reported	Effect of Change Higher/(Lower)	As Restated
Cost of sales	$ 2,847	$ (3)	$ 2,844
Selling, informational and administrative expenses	3,500	4	3,504
Research and development expenses	1,859	6	1,865
Restructuring charges and certain acquisition-related costs	149	(35)	114
Other (income)/deductions—net	51	28	79
Income from continuing operations before provision for taxes on income	3,585	—	3,585

	Nine Months Ended October 1, 2017		
(MILLIONS OF DOLLARS)	As Previously Reported	Effect of Change Higher/(Lower)	As Restated
Cost of sales	$ 7,980	$ (9)	$ 7,972
Selling, informational and administrative expenses	10,233	16	10,249
Research and development expenses	5,346	21	5,367
Restructuring charges and certain acquisition-related costs	377	(110)	267
Other (income)/deductions—net	(16)	81	65
Income from continuing operations before provision for taxes on income	11,351	—	11,351

Adoption of the standards impacted our condensed consolidated balance sheet as follows:

		Effect of New Accounting Standards Higher/(Lower)				
(MILLIONS OF DOLLARS)	As Previously Reported Balance at December 31, 2017	Revenues	Financial Assets and Liabilities	Income Tax Accounting	Reclassification of Certain Tax Effects from AOCI	Balance at January 1, 2018
Trade accounts receivable	$ 8,221	$ 13	$ —	$ —	$ —	$ 8,234
Inventories	7,578	(11)	—	—	—	7,567
Current tax assets	3,050	(11)	—	(3)	—	3,036
Noncurrent deferred tax assets and other noncurrent tax assets	1,855	(17)	—	—	—	1,838
Other noncurrent assets	3,227	—	—	(204)	—	3,023
Other current liabilities	11,115	(123)	—	—	—	10,992
Noncurrent deferred tax liabilities	3,900	106	—	(18)	—	3,988
Other noncurrent liabilities	6,149	(459)	—	—	—	5,690
Retained earnings	85,291	450	419	(189)	495	86,466
Accumulated other comprehensive loss	(9,321)	—	(419)	—	(495)	(10,235)

Adoption of the standards related to the classification of certain transactions in the statement of cash flows and the presentation of restricted cash in the statement of cash flows impacted our condensed consolidated statement of cash flows as follows:

	Nine Months Ended October 1, 2017			
		Effect of New Accounting Standards Inflow/(Outflow)		
(MILLIONS OF DOLLARS)	As Previously Reported	Cash Flow Classification	Restricted Cash	As Restated
Operating Activities				
Other adjustments, net	$ (561)	$ (43)	$ —	$ (604)
Other changes in assets and liabilities, net of acquisitions and divestitures	(3,644)	—	28	(3,616)
Investing Activities				
Proceeds from redemptions/sales of short-term investments	5,783	—	(5)	5,778
Proceeds from redemptions/sales of long-term investments	2,417	—	(14)	2,403
Financing Activities				
Principal payments on short-term borrowings	(7,691)	33	—	(7,659)
Net proceeds from short-term borrowings with original maturities of three months or less	555	10	—	566
Net increase in cash and cash equivalents and restricted cash and cash equivalents	184	—	9	193
Cash and cash equivalents and restricted cash and cash equivalents, beginning	2,595	—	70	2,666
Cash and cash equivalents and restricted cash and cash equivalents, ending	2,779	—	79	2,858

The following table provides a reconciliation of cash, cash equivalents and restricted cash reported within the condensed consolidated balance sheet that sum to the total of the same amounts shown in the condensed consolidated statements of cash flows:

(MILLIONS OF DOLLARS)	September 30, 2018	December 31, 2017
Cash and cash equivalents	$ 3,559	$ 1,342
Restricted cash and cash equivalents in *Short-term investments*	40	—
Restricted cash and cash equivalents in *Long-term investments*	59	—
Restricted cash and cash equivalents in *Other current assets*	—	14
Restricted cash and cash equivalents in *Other noncurrent assets*	—	75
Total cash and cash equivalents and restricted cash and cash equivalents shown in the condensed consolidated balance sheets	$ 3,658	$ 1,431

Amounts included in restricted cash represent those required to be set aside by a contractual agreement in connection with ongoing litigation or to secure delivery of Pfizer medicines at the agreed upon terms. The restriction will lapse upon the resolution of the litigation or the proper delivery of the medicines.

C. Revenues

On January 1, 2018, we adopted a new accounting standard for revenue recognition. For further information, see *Note 1B* .

We recorded direct product sales and/or alliance revenues of more than $1 billion for each of nine products in 2017. These direct products sales and/or alliance product revenues represented 46% of our revenues in 2017. The loss or expiration of intellectual property rights can have a significant adverse effect on our revenues as our contracts with customers will generally be at lower selling prices due to added competition and we generally provide for higher sales returns during the period in which individual markets begin to near the loss or expiration of intellectual property rights. Our Consumer Healthcare business includes OTC brands with a focus on dietary supplements, pain management, gastrointestinal and respiratory and personal care. According to Euromonitor International's retail sales data, in 2017, our Consumer Healthcare business was the fifth-largest branded multi-national, OTC consumer healthcare business in the world and produced two of the ten largest selling consumer

healthcare brands (*Centrum* and *Advil*) in the world. We sell biopharmaceutical products after patent expiration, and under patent, and, to a much lesser extent, consumer healthcare products worldwide to developed and emerging market countries.

Revenue Recognition —We record revenues from product sales when there is a transfer of control of the product from us to the customer. We determine transfer of control based on when the product is shipped or delivered and title passes to the customer.

- *Customers* —Our biopharmaceutical products are sold principally to wholesalers but we also sell directly to retailers, hospitals, clinics, government agencies and pharmacies, and, in the case of our vaccine products in the U.S., we primarily sell directly to the CDC, wholesalers and individual provider offices. Our consumer healthcare customers include retailers and, to a lesser extent, wholesalers and distributors.

  Biopharmaceutical products that ultimately are used by patients are generally covered under governmental programs, managed care programs and insurance programs, including those managed through pharmacy benefit managers, and are subject to sales allowances and/or rebates payable directly to those programs. Those sales allowances and rebates are generally negotiated, but government programs may have legislated amounts by type of product (e.g., patented or unpatented).
- *Our Sales Contracts* —Sales on credit are typically under short-term contracts. Collections are based on market payment cycles common in various markets, with shorter cycles in the U.S. Sales are adjusted for sales allowances, chargebacks, rebates and sales returns and cash discounts. Sales returns occur due to loss of exclusivity, product recalls or a changing competitive environment.
- *Deductions from Revenues* — Our gross product revenues are subject to a variety of deductions, which generally are estimated and recorded in the same period that the revenues are recognized. Such variable consideration represents chargebacks, rebates, sales allowances and sales returns. These deductions represent estimates of the related obligations and, as such, knowledge and judgment is required when estimating the impact of these revenue deductions on gross sales for a reporting period.

Specifically:

- In the U.S., we sell our products to distributors and hospitals under our sales contracts. However, we also have contracts with managed care or pharmacy benefit managers and legislatively mandated contracts with the federal and state governments under which we provide rebates to them based on medicines utilized by the lives they cover. We record provisions for Medicare, Medicaid, and performance-based contract pharmaceutical rebates based upon our experience ratio of rebates paid and actual prescriptions written during prior quarters. We apply the experience ratio to the respective period's sales to determine the rebate accrual and related expense. This experience ratio is evaluated regularly to ensure that the historical trends are as current as practicable. We estimate discounts on branded prescription drug sales to Medicare Part D participants in the Medicare "coverage gap," also known as the "doughnut hole," based on the historical experience of beneficiary prescriptions and consideration of the utilization that is expected to result from the discount in the coverage gap. We evaluate this estimate regularly to ensure that the historical trends and future expectations are as current as practicable. For performance-based contract rebates, we also consider current contract terms, such as changes in formulary status and rebate rates.
- Outside the U.S., the majority of our pharmaceutical sales allowances are contractual or legislatively mandated and our estimates are based on actual invoiced sales within each period, which reduces the risk of variations in the estimation process. In certain European countries, rebates are calculated on the government's total unbudgeted pharmaceutical spending or on specific product sales thresholds and we apply an estimated allocation factor against our actual invoiced sales to project the expected level of reimbursement. We obtain third-party information that helps us to monitor the adequacy of these accruals.
- Provisions for pharmaceutical chargebacks (primarily reimbursements to U.S. wholesalers for honoring contracted prices to third parties) closely approximate actual amounts incurred, as we settle these deductions generally within two to five weeks of incurring the liability.
- Provisions for pharmaceutical sales returns are based on a calculation for each market that incorporates the following, as appropriate: local returns policies and practices; historical returns as a percentage of sales; an understanding of the reasons for past returns; estimated shelf life by product; an estimate of the amount of time between shipment and return or lag time; and any other factors that could impact the estimate of future returns, such as loss of exclusivity, product recalls or a changing competitive environment. Generally, returned products are destroyed, and customers are refunded the sales price in the form of a credit.
- We record sales incentives as a reduction of revenues at the time the related revenues are recorded or when the incentive is offered, whichever is later. We estimate the cost of our sales incentives based on our historical experience with similar incentives programs to predict customer behavior.

Our accruals for Medicare rebates, Medicaid and related state program rebates, performance-based contract rebates, chargebacks, sales allowances and sales returns and cash discounts totaled $5.5 billion as of September 30, 2018 and $4.9 billion as of December 31, 2017 .

The following table provides information about the balance sheet classification of these accruals:

(MILLIONS OF DOLLARS)	September 30, 2018	December 31, 2017
Reserve against *Trade accounts receivable, less allowance for doubtful accounts*	$ 1,297	$ 1,352
Other current liabilities :		
Accrued rebates	3,235	2,674
Other accruals	641	512
Other noncurrent liabilities	374	385
Total accrued rebates and other accruals	$ 5,548	$ 4,923

Amounts recorded for revenue deductions can result from a complex series of judgments about future events and uncertainties and can rely heavily on estimates and assumptions. On a quarterly basis, our adjustments of estimates to reflect actual results generally have been less than 1% of revenues, and have resulted in either a net increase or a net decrease in *Revenues* . Product-specific rebates, however, can have a significant impact on year-over-year individual product growth trends.

Taxes collected from customers relating to product sales and remitted to governmental authorities are excluded from *Revenues* .

D. Collaborative Arrangements

Payments to and from our collaboration partners are presented in our condensed consolidated statements of income based on the nature of the arrangement (including its contractual terms), the nature of the payments and applicable accounting guidance. Under co-promotion agreements, we record the amounts received from our collaboration partners as alliance revenues, a component of *Revenues,* when our collaboration partners are the principal in the transaction and we receive a share of their net sales or profits. Alliance revenues are recorded as we perform co-promotion services for the collaboration and the collaboration partners sell the products to their customers within the applicable period. The related expenses for selling and marketing these products are included in *Selling, informational and administrative expenses.* In collaborative arrangements where we manufacture a product for our collaboration partners, we record revenues when we transfer control of the product to our collaboration partners. All royalty payments to collaboration partners are included in *Cost of sales* . Royalty payments received from collaboration partners are included in *Other (income)/deductions—net.*

Reimbursements to or from our collaboration partners for development costs are recorded net in *Research and development expenses* . Upfront payments and pre-approval milestone payments due from us to our collaboration partners in development stage collaborations are recorded as *Research and development expenses* . Milestone payments due from us to our collaboration partners after regulatory approval has been attained for a medicine are recorded in *Identifiable intangible assets—Developed technology rights* . Upfront and pre-approval milestone payments earned from our collaboration partners by us are recognized in *Other (income)/deductions—net* over the development period for the collaboration products, when our performance obligations include providing R&D services to our collaboration partners. Upfront, pre-approval and post-approval milestone payments earned by us may be recognized in *Other (income)/deductions—net* immediately when earned or over other periods depending upon the nature of our performance obligations in the applicable collaboration. Where the milestone event is regulatory approval for a medicine, we generally recognize milestone payments due to us in the transaction price when regulatory approval in the applicable jurisdiction has been attained. We may recognize milestone payments due to us in the transaction price earlier than the milestone event in certain circumstances when recognition of the income would not be probable of a significant reversal.

On January 1, 2018, we adopted a new accounting standard on revenue recognition (see *Note 1B*). As a result of the adoption, we recognized the following cumulative effect adjustments related to collaboration arrangements to *Retained earnings* :

- $394 million (pre-tax) for collaborative arrangements where upfront, pre-approval and regulatory approval milestone payments received from our collaboration partners are recognized in *Other (income)/deductions—net* over a reduced period. Under the new standard, the income from upfront and pre-approval milestone payments due to us is typically recognized over the development period for the collaboration when our performance obligation, in addition to granting a license, is to provide research and development services to our collaboration partners, and major regulatory approval milestones are typically recognized immediately when earned as the related development period has ended. The income from upfront and milestone payments is typically recognized immediately as earned if our performance obligation, in addition to granting a license, is

only for commercialization activities. Under the old standard, this income was recognized over the combined development and estimated commercialization (including co-promotion) period for the collaboration products.

- $82 million (pre-tax) for collaborative arrangements where we manufacture products for our collaboration partners and recognize *Revenues* and *Cost of sales* for product shipments at an earlier point in time. Under the new standard, revenue is recognized when we transfer control of the products to our collaboration partners. Under the old standard, revenue was recognized when our collaboration partners sell the products and transfer title to their third party customers.

Note 2. Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment

A. Acquisition

AstraZeneca's Small Molecule Anti-Infectives Business (EH)

On December 22, 2016, which fell in the first fiscal quarter of 2017 for our international operations, we acquired the development and commercialization rights to AstraZeneca's small molecule anti-infectives business, primarily outside the U.S., including the commercialization and development rights to the approved EU drug Zavicefta™ (ceftazidime-avibactam), the marketed agents Merrem™/Meronem™ (meropenem) and Zinforo™ (ceftaroline fosamil), and the clinical development assets ATM-AVI and CXL (ceftaroline fosamil-AVI). In 2017, under the terms of the agreement, we made payments of approximately $605 million to AstraZeneca related to the transaction. We made an additional milestone payment of $125 million in our first fiscal quarter of 2018 and we will make a deferred payment of $175 million to AstraZeneca in January 2019. In addition, we may be required to pay an additional milestone payment of $75 million if the related milestone is achieved prior to December 31, 2021, and up to $600 million if sales of Zavicefta™ exceed certain thresholds prior to January 1, 2026, as well as tiered royalties on sales of Zavicefta™ and ATM-AVI in certain markets for a period ending on the later of 10 years from first commercial sale or the loss of patent protection or loss of regulatory exclusivity. The total royalty payments are unlimited during the royalty term and the undiscounted payments are expected to be in the range of approximately $292 million to $512 million . The total fair value of consideration transferred for AstraZeneca's small molecule anti-infectives business was approximately $1,040 million inclusive of cash paid and the fair value of contingent consideration. In connection with this acquisition, we recorded $894 million in *Identifiable intangible assets* , consisting of $728 million in *Developed technology rights* and $166 million in *IPR&D* . We also recorded $92 million in *Other current assets* related to the economic value of inventory which was retained by AstraZeneca for sale on our behalf, $73 million in *Goodwill* and $19 million of net deferred tax liabilities. The final allocation of the consideration transferred to the assets acquired and the liabilities assumed has been completed.

B. Divestitures

Sale of Hospira Infusion Systems Net Assets to ICU Medical, Inc. (EH)

On October 6, 2016, we announced that we entered into a definitive agreement under which ICU Medical agreed to acquire all of our global infusion systems net assets, HIS, for approximately $1 billion in cash and ICU Medical common stock . HIS includes IV pumps, solutions, and devices. As a result of the performance of HIS relative to ICU Medical's expectations, on January 5, 2017, we entered into a revised agreement with ICU Medical under which ICU Medical would acquire HIS for up to approximately $900 million , composed of cash and contingent cash consideration, ICU Medical common stock and seller financing.

The revised transaction closed on February 3, 2017. At closing, we received 3.2 million newly issued shares of ICU Medical common stock (as originally agreed), which we initially valued at approximately $428 million (based upon the closing price of ICU Medical common stock on the closing date less a discount for lack of marketability) and which are reported as equity securities at fair value in *Long-term investments* on the condensed consolidated balance sheet. In August 2018, we sold 700,000 shares of ICU Medical common stock for which we recognized a gain during the period of $50 million , reflecting the increase in fair value of the equity investment since the beginning of the year, most of which was previously recognized as 2018 unrealized gains. In addition, we continue to hold 2.5 million shares of ICU Medical common stock and we recognized unrealized gains of $24 million in the third quarter of 2018 and unrealized gains of $229 million in the first nine months of 2018 related to these remaining shares. We also received a promissory note in the amount of $75 million , which was repaid in full as of December 31, 2017, and net cash of approximately $200 million before customary adjustments for net working capital, which is reported in Other investing activities, net on the condensed consolidated statement of cash flows for the nine months ended October 1, 2017 . In addition, we are entitled to receive a contingent amount of up to an additional $225 million in cash based on ICU Medical's achievement of certain cumulative performance targets for the combined company through December 31, 2019. After our recent sale of ICU Medical shares, we own approximately 12% of ICU Medical. We recognized pre-tax income of $2 million in the third quarter of 2018 and pre-tax income of $1 million in the first nine months of 2018 , and

we recognized pre-tax income of $12 million in the third quarter of 2017 and pre-tax losses of $52 million in the first nine months of 2017 in *Other (income)/deductions—net,* representing adjustments to amounts previously recorded in 2016 to write down the HIS net assets to fair value less costs to sell. For additional information, see *Note 4* and Notes to Consolidated Financial Statements— *Note 2. Acquisitions, Sale of Hospira Infusion Systems Net Assets, Research and Development and Collaborative Arrangements, Equity-Method Investments and Cost-Method Investment* in Pfizer's 2017 Financial Report.

While we have received the full purchase price excluding the contingent amount as of the February 3, 2017 closing, the sale of the HIS net assets was not fully completed in certain non-U.S. jurisdictions as of the third quarter of 2018 due to temporary regulatory or operational constraints. In these jurisdictions, which represent a relatively small portion of the HIS net assets, we continued to operate the net assets for the net economic benefit of ICU Medical, and we were indemnified by ICU Medical against risks associated with such operations during the interim period, subject to our obligations under the definitive transaction agreements. We have previously treated these jurisdictions as sold for accounting purposes.

In connection with the sale transaction, we entered into certain transitional agreements designed to facilitate the orderly transition of the HIS net assets to ICU Medical. These agreements primarily relate to administrative services, which are generally to be provided for a period of up to 24 months after the closing date. We will also manufacture and supply certain HIS products for ICU Medical and ICU Medical will manufacture and supply certain retained Pfizer products for us after closing, generally for a term of five years. These agreements are not material to Pfizer and none confers upon us the ability to influence the operating and/or financial policies of ICU Medical subsequent to the sale.

Contribution Agreement Between Pfizer and Allogene Therapeutics, Inc. (WRD)

In April 2018, Pfizer and Allogene announced that the two companies entered into a contribution agreement for Pfizer's portfolio of assets related to allogeneic CAR T therapy, an investigational immune cell therapy approach to treating cancer. Under this agreement, Allogene received from Pfizer rights to pre-clinical and clinical CAR T assets, all of which were previously licensed to Pfizer from French cell therapy company, Cellectis, beginning in 2014 and French pharmaceutical company, Servier, beginning in 2015. Allogene assumed responsibility for all potential financial obligations to both Cellectis and Servier. Pfizer will continue to participate financially in the development of the CAR T portfolio through an ownership stake in Allogene. Separately, Pfizer continues to maintain its approximate 7% ownership stake in Cellectis that was obtained in 2014 as part of the licensing agreement in which Pfizer obtained exclusive rights to pursue the development and commercialization of certain Cellectis CAR T therapies in exchange for an upfront payment of $80 million , as well as potential future development, regulatory and commercial milestone payments and royalties. In connection with the Allogene transaction, Pfizer recognized a non-cash $50 million pre-tax gain in *Other (income)/deductions—net* in the second quarter of 2018 , representing the difference between the $127 million fair value of the equity investment received and the book value of assets transferred (including an allocation of goodwill) (see *Note 4*).

In October 2018, Allogene consummated an initial public offering of new shares of its common stock, which resulted in Pfizer's preferred stock converting into common stock and a decrease in our ownership percentage from approximately 25% to approximately 19% . The closing price on the day of the initial public offering was $25 per share. Beginning as of the date of the initial public offering, our investment in Allogene, which is reported at $127 million in *Long-term investments* on the condensed consolidated balance sheet as of September 30, 2018, will be measured at fair value with changes in fair value recognized in net income.

Sale of Phase 2b Ready AMPA Receptor Potentiator for CIAS to Biogen Inc. (WRD)

In April 2018, we sold our Phase 2b ready AMPA receptor potentiator for CIAS to Biogen. We received $75 million upfront and have the opportunity to receive up to $515 million in future development and commercialization milestones, as well as tiered royalties in the low-to-mid-teen percentages. We recognized $75 million in *Other (income)/deductions—net* in the second quarter of 2018 (see *Note 4*). We will record the milestones and royalties to *Other (income)/deductions—net* when due, or earlier if we have sufficient experience to determine such amounts are not probable of significant reversal.

Divestiture of Neuroscience Assets (WRD)

In September 2018, we and Bain Capital entered into a transaction to create a new biopharmaceutical company, Cerevel, to continue development of a portfolio of clinical and preclinical stage neuroscience assets primarily targeting disorders of the central nervous system including Parkinson's disease, epilepsy, Alzheimer's disease, schizophrenia and addiction. These assets were part of the neuroscience discovery and early development efforts, which we announced we were ending in January 2018. In connection with this transaction, we out-licensed the portfolio to Cerevel in exchange for a 25% ownership stake in Cerevel's parent company, Cerevel Therapeutics, Inc., and potential future regulatory and commercial milestone payments and royalties. Bain Capital has committed to invest $350 million to develop the portfolio, with the potential for additional funding as the assets advance. In connection with the transaction, we recognized a non-cash $343 million pre-tax gain in *Other (income)/*

deductions—net , representing the fair value of the equity investment received as the assets transferred had a book value of $0 (see *Note 4*). Our investment in Cerevel Therapeutics, Inc. is reported in *Long-term investments* on the consolidated balance sheet as of September 30, 2018.

C. Licensing Arrangements

Shire International GmbH (IH)

In 2016, we out-licensed PF-00547659, an investigational biologic being evaluated for the treatment of moderate-to-severe inflammatory bowel disease, including ulcerative colitis and Crohn's disease, to Shire for an upfront payment of $90 million , up to $460 million in development and sales-based milestone payments and potential future royalty payments on commercialized products. The $90 million upfront payment was initially deferred and recognized in *Other (income)/deductions—net* ratably through December 2017. In the first quarter of 2018, we recognized $75 million in *Other (income)/deductions—net* for a milestone payment received from Shire related to their first dosing of a patient in a Phase 3 clinical trial of the compound for the treatment of ulcerative colitis, and in the third quarter of 2018, we recognized $35 million in *Other (income)/deductions—net* for a milestone payment received from Shire related to their first dosing of a patient in a Phase 3 clinical trial of the compound for the treatment of Crohn's disease (see *Note 4*).

BionTech AG (WRD)

In August 2018, a multi-year R&D arrangement went into effect between BionTech AG (BionTech), a privately held company, and Pfizer to develop mRNA-based vaccines for prevention of influenza (flu). In September 2018, we made an upfront payment of $50 million to BionTech, which was recorded in *Research and development expenses,* and BionTech is eligible to receive up to an additional $325 million in future development and sales based milestones and future royalty payments associated with worldwide sales. As part of the transaction, we also purchased 169,670 newly-issued ordinary shares of BionTech for $50 million in the third quarter of 2018, which are reported in *Long-term investments* in the condensed consolidated balance sheet as of September 30, 2018.

D. Collaboration Arrangements

Collaboration with Merck & Co., Inc. (IH)

Under a worldwide collaboration agreement, except for Japan, we collaborated with Merck on the clinical development of ertugliflozin and ertugliflozin-containing fixed-dose combinations with metformin and Januvia (sitagliptin) tablets, which were approved by the FDA in December 2017 and the European Commission in March 2018 as Steglatro, Segluromet and Steglujan. Merck will exclusively promote Steglatro and the two fixed-dose combination products and we will share revenues and certain costs with Merck on a 60% / 40% basis, with Pfizer having the 40% share. Pfizer records its share of the collaboration revenues as product sales as we supply the ertugliflozin active pharmaceutical ingredient to Merck for use in the alliance products.

In the first quarter of 2017 , we received a $90 million milestone payment from Merck upon the FDA's acceptance for review of the NDAs for ertugliflozin and two fixed-dose combinations (ertugliflozin plus Januvia (sitagliptin) and ertugliflozin plus metformin), which, as of December 31, 2017, was deferred and primarily reported in *Other noncurrent liabilities,* and through December 31, 2017, was being recognized in *Other (income)/deductions—net* over a multi-year period. As of December 31, 2017, we were due a $60 million milestone payment from Merck, which we received in the first quarter of 2018, in conjunction with the approval of ertugliflozin by the FDA. As of December 31, 2017, the $60 million due from Merck was deferred and primarily reported in *Other noncurrent liabilities* . In the first quarter of 2018, in connection with the approval of ertugliflozin in the EU, we recognized a $40 million milestone payment from Merck in *Other (income)/deductions—net* (see *Note 4*). We are eligible for additional payments associated with the achievement of future commercial milestones. In the first quarter of 2018, in connection with the adoption of a new accounting standard, as of January 1, 2018, the $60 million of deferred income and approximately $85 million of the $90 million of deferred income associated with the above-mentioned milestone payments were recorded to and included in the $584 million cumulative effect adjustment to *Retained earnings* . See *Note 1B* for additional information.

Collaboration with Eli Lilly & Company (IH)

In 2013, we entered into a collaboration agreement with Lilly to jointly develop and globally commercialize Pfizer's tanezumab, which provides that Pfizer and Lilly will equally share product-development expenses as well as potential revenues and certain product-related costs. We received a $200 million upfront payment from Lilly in accordance with the collaboration agreement between Pfizer and Lilly, which was deferred and primarily reported in *Other noncurrent liabilities,* and through December 31, 2017, was being recognized in *Other (income)/deductions—net* over a multi-year period beginning in the second quarter of 2015. Pfizer and Lilly resumed the Phase 3 chronic pain program for tanezumab in July 2015. The FDA granted Fast Track designation for tanezumab for the treatment of chronic pain in patients with osteoarthritis and chronic low back pain in June 2017. Under the collaboration agreement with Lilly, we are eligible to receive additional payments from Lilly upon the achievement of specified regulatory and commercial milestones.

In the first quarter of 2018, in connection with the adoption of a new accounting standard, as of January 1, 2018, approximately $107 million of deferred income associated with the above-mentioned upfront payment was recorded to and included in the $584 million cumulative effect adjustment to *Retained earnings* . See *Note 1B* for additional information. Approximately $33 million of the upfront payment continues to be deferred, of which approximately $24 million is reported in *Other current liabilities* and approximately $9 million is reported in *Other noncurrent liabilities* as of September 30, 2018 . This amount is expected to be recognized in *Other (income)/deductions—net* over the remaining development period for the product between 2018 and 2020.

E. Privately Held Investment

AM-Pharma B.V. (WRD)

In April 2015, we acquired a minority equity interest in AM-Pharma B.V., a privately-held Dutch biopharmaceutical company focused on the development of human recombinant Alkaline Phosphatase (recAP) for inflammatory diseases, and secured an exclusive option to acquire the remaining equity in the company. The option became exercisable after completion of a Phase 2 trial of recAP for the treatment of Acute Kidney Injury related to sepsis in the first quarter of 2018. We declined to exercise the option and the option expired unexercised during the second quarter of 2018.

Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives

We incur significant costs in connection with acquiring, integrating and restructuring businesses and in connection with our global cost-reduction/productivity initiatives. For example:

- In connection with acquisition activity, we typically incur costs associated with executing the transactions, integrating the acquired operations (which may include expenditures for consulting and the integration of systems and processes), and restructuring the combined company (which may include charges related to employees, assets and activities that will not continue in the combined company); and
- In connection with our cost-reduction/productivity initiatives, we typically incur costs and charges associated with site closings and other facility rationalization actions, workforce reductions and the expansion of shared services, including the development of global systems.

All of our businesses and functions may be impacted by these actions, including sales and marketing, manufacturing and R&D, as well as groups such as information technology, shared services and corporate operations.

In connection with our acquisition of Hospira in September 2015, we focused our efforts on achieving an appropriate cost structure for the combined company. We expect to incur costs of approximately $1 billion (not including costs of $215 million associated with the return of acquired IPR&D rights as described in the *Current-Period Key Activities* section of Notes to Consolidated Financial Statements— *Note 3 . Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* in our 2017 Financial Report) associated with the integration of Hospira. The majority of these costs were incurred within the three -year period post-acquisition.

As a result of the evaluation performed in connection with our decision in September 2016 to not pursue, at that time, splitting IH and EH into two separate publicly-traded companies, we identified new opportunities to potentially achieve greater optimization and efficiency to become more competitive in our business. Therefore, in early 2017 , we initiated new enterprise-wide cost reduction/productivity initiatives, which we expect to substantially complete by the end of 2019. These initiatives encompass all areas of our cost base and include:

- Optimization of our manufacturing plant network to support IH and EH products and pipelines. During 2017-2019, we expect to incur costs of approximately $700 million related to this initiative. Through September 30, 2018 , we incurred approximately $322 million associated with this initiative.
- Activities in non-manufacturing related areas, which include further centralization of our corporate and platform functions, as well as other activities where opportunities are identified. During 2017-2019, we expect to incur costs of approximately $450 million related to this initiative. Through September 30, 2018 , we incurred approximately $252 million associated with this initiative.

The costs expected to be incurred during 2017-2019, of approximately $1.2 billion for the above-mentioned programs (but not including the costs associated with the Hospira integration), include restructuring charges, implementation costs and additional depreciation—asset restructuring. Of this amount, we expect that about 20% of the total charges will be non-cash.

Current-Period Key Activities

For the first nine months of 2018 , we incurred costs of $226 million associated with the 2017-2019 program, $186 million associated with the integration of Hospira and $35 million associated with all other acquisition-related initiatives.

The following table provides the components of costs associated with acquisitions and cost-reduction/productivity initiatives:

	Three Months Ended		Nine Months Ended	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Restructuring (credits)/charges:				
Employee terminations	$ (24)	$ (55)	$ (53)	$ (113)
Asset impairments [a]	12	101	8	126
Exit costs	14	10	14	16
Restructuring charges/(credits) [b]	1	56	(32)	28
Transaction costs [c]	1	(14)	1	4
Integration costs [d]	82	73	202	235
Restructuring charges and certain acquisition-related costs	85	114	172	267
Net periodic benefit costs recorded in *Other (income)/deductions—net* [e]	41	35	103	110
Additional depreciation—asset restructuring, virtually all of which is recorded in *Cost of sales* [f]	12	39	43	74
Implementation costs recorded in our condensed consolidated statements of income as follows [g] :				
Cost of sales	21	26	57	77
Selling, informational and administrative expenses	17	22	51	46
Research and development expenses	9	9	22	26
Total implementation costs	48	57	130	150
Total costs associated with acquisitions and cost-reduction/productivity initiatives	$ 186	$ 245	$ 447	$ 601

[a] The asset impairment charges for the three and nine months ended October 1, 2017 are largely associated with our acquisitions of Hospira and Medivation.

[b] In the third quarter of 2018 , restructuring charges are primarily due to accruals for exit costs and asset write downs related to our acquisition of Hospira, partially offset by the reversal of previously recorded accruals for employee termination costs. In the first nine months of 2018 , restructuring credits are mostly related to the reversal of previously recorded accruals for employee termination costs. In the three and nine months ended October 1, 2017 , restructuring charges were mainly associated with our acquisitions of Hospira and Medivation, partially offset by credits associated with cost-reduction and productivity initiatives not associated with acquisitions that mostly related to the reversal of previously recorded accruals for employee termination costs. *Employee terminations* primarily include revisions of our estimates of severance benefits. Employee termination costs are generally recorded when the actions are probable and estimable and include accrued severance benefits, many of which may be paid out during periods after termination.

The restructuring activities for 2018 are associated with the following:

- For the third quarter of 2018 , IH ($13 million credit); EH ($7 million charge); manufacturing operations ($1 million charge); WRD/GPD ($3 million charge); and Corporate ($3 million charge).
- For the first nine months of 2018 , IH ($25 million credit); EH ($5 million credit); WRD/GPD ($1 million charge); manufacturing operations ($16 million charge); and Corporate ($19 million credit).

The restructuring activities for 2017 are associated with the following:

- For the third quarter of 2017 , IH ($1 million charge); EH ($1 million charge); WRD/GPD ($2 million charge); manufacturing operations ($40 million charge); and Corporate ($12 million charge).
- For the first nine months of 2017 , IH ($1 million credit); EH ($11 million credit); WRD/GPD ($24 million credit); manufacturing operations ($48 million charge); and Corporate ($15 million charge).

[c] Transaction costs represent external costs for banking, legal, accounting and other similar services, which in the third quarter of 2017 reflect the reversal of an accrual related to the acquisition of Medivation. Transaction costs for the first nine months of 2017 were directly related to our acquisitions of Hospira, Anacor and Medivation.

[d] Integration costs represent external, incremental costs directly related to integrating acquired businesses, and primarily include expenditures for consulting and the integration of systems and processes. In the third quarter and first nine months of 2018 , integration costs were primarily related to our acquisition of Hospira. In the third quarter and first nine months of 2017 , integration costs primarily relate to our acquisitions of Hospira and Medivation. The first nine months of 2017 also include a net gain of $12 million related to the settlement of the Hospira U.S. qualified defined benefit pension plan (see *Note 10*).

[e] In the three and nine months ended September 30, 2018 , primarily represents the net pension curtailments and settlements included in *Other (income)/deductions—net* upon the adoption of a new accounting standard in the first quarter of 2018. In the three and nine months ended October 1, 2017 , primarily represents the net pension curtailments and settlements, partially offset by net periodic benefit credits, excluding service costs, related to our acquisition of Hospira, both of which were reclassified to *Other (income)/deductions—net* as a result of the retrospective adoption of a new accounting standard in the first quarter of 2018. These credits included a net settlement gain, partially offset by accelerated amortization of actuarial losses and prior service costs upon the settlement of the remaining obligation associated with the Hospira U.S. qualified defined benefit pension plan. For additional information, see *Note 1B* and *Note 10* .

[f] Additional depreciation—asset restructuring represents the impact of changes in the estimated useful lives of assets involved in restructuring actions.

[g] Implementation costs represent external, incremental costs directly related to implementing our non-acquisition-related cost-reduction/productivity initiatives.

The following table provides the components of and changes in our restructuring accruals:

(MILLIONS OF DOLLARS)	Employee Termination Costs	Asset Impairment Charges	Exit Costs	Accrual
Balance, December 31, 2017 [a]	$ 1,039	$ —	$ 66	$ 1,105
Provision/(Credit)	(53)	8	14	(32)
Utilization and other [b]	(235)	(8)	(34)	(277)
Balance, September 30, 2018 [c]	$ 750	$ —	$ 46	$ 796

[a] Included in *Other current liabilities* ($643 million) and *Other noncurrent liabilities* ($462 million).

[b] Includes adjustments for foreign currency translation.

[c] Included in *Other current liabilities* ($397 million) and *Other noncurrent liabilities* ($399 million).

Note 4. Other (Income)/Deductions—Net

The following table provides components of *Other (income)/deductions—net* :

	Three Months Ended		Nine Months Ended	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Interest income [a]	$ (82)	$ (99)	$ (240)	$ (275)
Interest expense [a]	310	320	946	940
Net interest expense	228	220	706	666
Royalty-related income	(143)	(140)	(360)	(331)
Net gains on asset disposals [b]	(4)	(13)	(19)	(36)
Net gains recognized during the period on investments in equity securities [c]	(94)	(45)	(460)	(111)
Net realized (gains)/losses on sales of investments in debt securities	8	(23)	12	(45)
Income from collaborations, out-licensing arrangements and sales of compound/product rights [d]	(139)	(78)	(455)	(163)
Net periodic benefit costs/(credits) other than service costs [e]	(65)	28	(231)	81
Certain legal matters, net [f]	37	183	(70)	194
Certain asset impairments [g]	(1)	130	40	143
Adjustments to loss on sale of HIS net assets [h]	(2)	(12)	(1)	52
Business and legal entity alignment costs [i]	—	16	4	54
Other, net [j]	(239)	(186)	(309)	(439)
Other (income)/deductions—net	$ (414)	$ 79	$ (1,143)	$ 65

[a] Interest income decreased in the third quarter and first nine months of 2018 , primarily driven by a lower investment balance. Interest expense decreased in the third quarter of 2018 , primarily as a result of refinancing activity that occurred in the fourth quarter of 2017 and a credit to interest expense due to settlement of a tax indemnification case. Interest expense increased for the first nine months of 2018 , primarily as a result of higher short-term interest rates, offset, in part, by refinancing activity that occurred in the fourth quarter of 2017.

[b] In the first nine months of 2017 , primarily includes a realized gain on sale of property of $52 million , partially offset by a realized net loss of $30 million related to the sale of our 40% ownership investment in Teuto, including the extinguishment of a put option for the then remaining 60% ownership interest.

[c] The net gains on investments in equity securities for the third quarter of 2018 include unrealized net gains on equity securities of $8 million and, for the first nine months of 2018 , include unrealized net gains on equity securities of $344 million , reflecting the adoption of a new accounting standard in the first quarter of 2018. We continue to hold 2.5 million shares of ICU Medical common stock and we recognized unrealized gains of $24 million in the third quarter of 2018 and unrealized gains of $229 million in the first nine months of 2018 related to these remaining shares. Prior to the adoption of a new accounting standard in the first quarter of 2018, net unrealized gains and losses on virtually all equity securities with readily determinable fair values were reported in *Accumulated other comprehensive income* . For additional information, see *Note 1B, Note 2B* and *Note 7B* .

[d] Includes income from upfront and milestone payments from our collaboration partners and income from out-licensing arrangements and sales of compound/product rights. In the third quarter of 2018 , primarily includes, among other things, (i) $40 million in milestone income from a certain licensee, (ii) a $35 million milestone payment received from Shire related to their first dosing of a patient in a Phase 3 clinical trial of a compound out-licensed by Pfizer to Shire for the treatment of Crohn's disease and (iii) $45 million in gains related to sales of compound/product rights. In the first nine months of 2018 , primarily includes, among other things, (i) approximately $128 million in milestone income from multiple licensees, (ii) an upfront payment to us of $75 million for the sale of an AMPA receptor potentiator for CIAS to Biogen, (iii) $110 million in milestone payments received from Shire, of which $75 million was received in the first quarter of 2018 related to their first dosing of a patient in a Phase 3 clinical trial for the treatment of ulcerative colitis and $35 million was received from Shire related to their first dosing of a patient in a Phase 3 clinical trial for the treatment of Crohn's disease, (iv) a $40 million milestone payment from Merck in conjunction with the approval of ertugliflozin in the EU and (v) $45 million in gains related to sales of compound/product rights. In the third quarter of 2017 , primarily includes, among other things, $50 million in milestone income from a certain licensee and a $15 million gain related to the sale of compound/product rights. In the first nine months of 2017 , primarily includes, among other things, approximately $81 million in milestone income from multiple licensees and a $43 million gain related to the sale of compound/product rights. For additional information, see *Note 2B, Note 2C* and *Note 2D* .

[e] Represents the net periodic benefit costs/(credits), excluding service costs, as a result of the adoption of a new accounting standard in the first quarter of 2018. Effective January 1, 2018, the U.S. Pfizer Consolidated Pension Plan was frozen to future benefit accruals and for the third quarter and first nine months of 2018 , resulted in the recognition of lower net periodic benefit costs due to the extension of the amortization period for the actuarial losses. There was also a greater than expected gain on plan assets due to a higher plan asset base compared to the third quarter and first nine months of 2017. For additional information, see *Note 1B* and *Note 10* .

[f] For the first nine months of 2018 , the net credits primarily represent the reversal of a legal accrual where a loss was no longer deemed probable. In the third quarter and first nine months of 2017 , primarily includes a $94 million charge to resolve a class action lawsuit filed by direct purchasers relating to Celebrex, which was approved by the court in April 2018, and a $79 million charge to reflect damages awarded by a jury in a patent matter.

[g] In the first nine months of 2018 , primarily includes a $31 million intangible asset impairment charge recorded in the second quarter of 2018 related to an IH finite-lived developed technology right, acquired in connection with our acquisition of Anacor, for the treatment for toenail fungus marketed in the U.S. market only . The impairment charge recorded in the second quarter of 2018 related to IH reflects , among other things, updated commercial forecasts. In the third quarter and first nine months of 2017 , primarily includes an intangible asset impairment charge of $127 million related to developed technology rights, acquired in connection with our acquisition of Hospira, for a generic sterile injectable product for the treatment of edema associated with certain conditions.

The intangible asset impairment charge for the third quarter and first nine months of 2017 is associated with EH and reflects, among other things, updated commercial forecasts and an increased competitive environment.

(h) Represents adjustments to amounts previously recorded in 2016 to write down the HIS net assets to fair value less costs to sell related to the sale of HIS net assets to ICU Medical on February 3, 2017. For additional information, see *Note 2B* .

(i) Represents expenses for changes to our infrastructure to align our commercial operations of our current segments, including costs to internally separate our businesses into distinct legal entities, as well as to streamline our intercompany supply operations to better support each business.

(j) In the third quarter and first nine months of 2018 , includes a non-cash $343 million pre-tax gain associated with our transaction with Bain Capital to create a new biopharmaceutical company, Cerevel, to continue development of a portfolio of clinical and preclinical stage neuroscience assets primarily targeting disorders of the central nervous system (see *Note 2B*). The third quarter and first nine months of 2018 also include, among other things, dividend income of $91 million and $226 million , respectively, from our investment in ViiV, and charges of $122 million and $257 million , respectively, reflecting the change in the fair value of contingent consideration. The first nine months of 2018 also include a non-cash $50 million pre-tax gain on the contribution of Pfizer's allogeneic CAR T therapy development program assets obtained from Cellectis and Servier in connection with our contribution agreement entered into with Allogene in which Pfizer obtained a 25% ownership stake in Allogene (see *Note 2B*), and a non-cash $17 million pre-tax gain on the cash settlement of a liability that we incurred in April 2018 upon the EU approval of Mylotarg (see *Note 7E*). In the third quarter and first nine months of 2017 , includes, among other things, dividend income of $54 million and $211 million , respectively, from our investment in ViiV and income of $62 million from resolution of a contract disagreement.

The following table provides additional information about the intangible asset that was impaired during 2018 in *Other (income)/deductions:*

	Fair Value [a]				Nine Months Ended September 30, 2018
(MILLIONS OF DOLLARS)	Amount	Level 1	Level 2	Level 3	Impairment
Intangible assets—Developed technology right, finite-lived [b]	$ 35	$ —	$ —	$ 35	$ 31

(a) The fair value amount is presented as of the date of impairment, as these assets are not measured at fair value on a recurring basis.

(b) Reflects an intangible asset written down to fair value in the first nine months of 2018 . Fair value was determined using the income approach, specifically the multi-period excess earnings method, also known as the discounted cash flow method. We started with a forecast of all the expected net cash flows associated with the asset and then applied an asset-specific discount rate to arrive at a net present value amount. Some of the more significant estimates and assumptions inherent in this approach include: the amount and timing of the projected net cash flows, which includes the expected impact of competitive, legal and/or regulatory forces on the product; the discount rate, which seeks to reflect the various risks inherent in the projected cash flows; and the tax rate, which seeks to incorporate the geographic diversity of the projected cash flows.

Note 5. Tax Matters

A. Taxes on Income from Continuing Operations

In the fourth quarter of 2017, we recorded an estimate of certain tax effects of the TCJA, including the impact on deferred tax assets and liabilities from the reduction in the U.S. Federal corporate tax rate from 35% to 21% , the impact on valuation allowances and other state income tax considerations, the $15.2 billion repatriation tax liability on accumulated post-1986 foreign earnings for which we plan to elect payment over eight years through 2026 (with the first of eight installments due in April 2019) that is reported primarily in *Other taxes payable* , and deferred taxes on basis differences expected to give rise to future taxes on global intangible low-taxed income. In addition, we had provided deferred tax liabilities in the past on foreign earnings that were not indefinitely reinvested. As a result of the TCJA, we reversed an estimate of the deferred taxes that are no longer expected to be needed due to the change to the territorial tax system. The estimated amounts recorded may change in the future due to uncertain tax positions. With respect to the aforementioned repatriation tax liability related to the TCJA repatriation tax, our obligations may vary as a result of changes in our uncertain tax positions and/or availability of attributes such as foreign tax and other credit carryforwards.

The TCJA subjects a U.S. shareholder to current tax on global intangible low-taxed income earned by certain foreign subsidiaries. The FASB Staff Q&A, Topic 740, No. 5, *Accounting for Global Intangible Low-Taxed Income* , states that we are permitted to make an accounting policy election to either recognize deferred taxes for temporary basis differences expected to reverse as global intangible low-taxed income in future years or provide for the tax expense related to such income in the year the tax is incurred. We have elected to recognize deferred taxes for temporary differences expected to reverse as global intangible low-taxed income in future years. However, given the complexity of these provisions, we have not finalized our analysis. We were able to make a reasonable estimate of the deferred taxes on the temporary differences expected to reverse in the future and provided a provisional deferred tax liability of approximately $1 billion as of December 31, 2017. The provisional amount is based on the evaluation of certain temporary differences inside each of our foreign subsidiaries that are expected to reverse as global intangible low-taxed income. However, as we continue to evaluate the TCJA's global intangible low-taxed income provisions during the measurement period, we may revise the methodology used for determining the deferred tax liability associated with such income.

We believe that we have made reasonable estimates with respect to each of the above items, however, all of the amounts recorded remain provisional as we have not completed our analysis of the complex and far reaching effects of the TCJA. Further, we continue to consider our assertions on any remaining outside basis differences in our foreign subsidiaries as of

September 30, 2018 and have not completed our analysis. In the third quarter of 2018, we recorded a favorable adjustment to the provisional estimate of the impact of the legislation, primarily related to the remeasurement of deferred tax assets and liabilities as well as revised estimates of benefits related to certain tax initiatives. Under guidance issued by the staff of the SEC, we expect to finalize our accounting related to the tax effects of the TCJA on deferred taxes, valuation allowances, state tax considerations, the repatriation tax liability, global intangible low-taxed income, and any remaining outside basis differences in our foreign subsidiaries during the fourth quarter of 2018, as we complete the remainder of our tax return filings and as any interpretations or clarifications of the TCJA occur through further legislation or U.S. Treasury actions or other means.

Our effective tax rate for continuing operations was 1.6% for the third quarter of 2018 , compared to 20.3% for the third quarter of 2017 and was 9.9% for the first nine months of 2018 , compared to 20.1% for the first nine months of 2017 .

The lower effective tax rate for the third quarter and first nine months of 2018 in comparison with the same periods in 2017 was primarily due to:

- the adoption of a territorial system and the lower U.S. tax rate as a result of the December 2017 enactment of the TCJA as well as favorable adjustments to the provisional estimate of the impact of the legislation;
- the favorable change in the jurisdictional mix of earnings as a result of operating fluctuations in the normal course of business; as well as
- an increase in benefits associated with the resolution of certain tax positions pertaining to prior years primarily with various foreign tax authorities, and the expiration of certain statutes of limitations.

B. Deferred Taxes

We have not completed our analysis of the TCJA on our prior assertion of indefinitely reinvested earnings. Accordingly, we continue to evaluate our assertion with respect to our accumulated foreign earnings subject to the deemed repatriation tax and we also continue to evaluate the amount of earnings that are indefinitely reinvested. Additionally, we continue to evaluate our assertions on any remaining outside basis differences in our foreign subsidiaries as of September 30, 2018 as we have not finalized our analysis of the effects of all of the new provisions in the TCJA. As of September 30, 2018 , it is not practicable to estimate the additional deferred tax liability that would be recorded if the earnings subject to the deemed repatriation tax and any remaining outside basis differences as of September 30, 2018 are not indefinitely reinvested. In accordance with the authoritative guidance issued by the SEC Staff Accounting Bulletin 118, we expect to complete our analysis within the measurement period.

C. Tax Contingencies

We are subject to income tax in many jurisdictions, and a certain degree of estimation is required in recording the assets and liabilities related to income taxes. All of our tax positions are subject to audit by the local taxing authorities in each tax jurisdiction. These tax audits can involve complex issues, interpretations and judgments and the resolution of matters may span multiple years, particularly if subject to negotiation or litigation. Our assessments are based on estimates and assumptions that have been deemed reasonable by management, but our estimates of unrecognized tax benefits and potential tax benefits may not be representative of actual outcomes, and variation from such estimates could materially affect our financial statements in the period of settlement or when the statutes of limitations expire, as we treat these events as discrete items in the period of resolution.

The U.S. is one of our major tax jurisdictions, and we are regularly audited by the IRS:

- With respect to Pfizer, the IRS has issued a Revenue Agent’s Report (RAR) for tax years 2009-2010. We are not in agreement with the RAR and are currently appealing certain disputed issues. Tax years 2011-2015 are currently under audit. Tax years 2016-2018 are open but not under audit. All other tax years are closed.
- With respect to Hospira, the federal income tax audit of tax year 2014 through short-year 2015 was effectively settled in the second quarter of 2018. All other tax years are closed.
- With respect to Anacor and Medivation, the open tax years are not considered material to Pfizer.

In addition to the open audit years in the U.S., we have open audit years in other major tax jurisdictions, such as Canada (2013-2018), Japan (2017-2018), Europe (2011-2018, primarily reflecting Ireland, the United Kingdom, France, Italy, Spain and Germany), Latin America (1998-2018, primarily reflecting Brazil) and Puerto Rico (2011-2018).

D. Tax Provision/(Benefit) on Other Comprehensive Income/(Loss)

The following table provides the components of *Tax provision/(benefit) on other comprehensive income/(loss):*

	Three Months Ended		Nine Months Ended	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Foreign currency translation adjustments, net [a]	$ 14	$ (62)	$ 82	$ (192)
Unrealized holding gains/(losses) on derivative financial instruments, net	35	28	39	30
Reclassification adjustments for (gains)/losses included in net income	(28)	(29)	36	(169)
Reclassification adjustments of certain tax effects from AOCI to *Retained earnings* [b]	—	—	1	—
	7	(1)	77	(139)
Unrealized holding gains/(losses) on available-for-sale securities, net	20	37	(8)	93
Reclassification adjustments for gains included in net income	(6)	(49)	(8)	(45)
Reclassification adjustments for tax on unrealized gains from AOCI to *Retained earnings* [c]	—	—	(45)	—
	14	(12)	(62)	47
Benefit plans: actuarial gains/(losses), net	2	(37)	27	(15)
Reclassification adjustments related to amortization	15	60	43	152
Reclassification adjustments related to settlements, net	10	22	25	30
Reclassification adjustments of certain tax effects from AOCI to *Retained earnings* [b]	—	—	637	—
Other	11	(33)	18	(46)
	38	11	750	121
Benefit plans: prior service costs and other, net	—	—	—	—
Reclassification adjustments related to amortization	(11)	(17)	(33)	(50)
Reclassification adjustments related to curtailments, net	(1)	(1)	(4)	(5)
Reclassification adjustments of certain tax effects from AOCI to *Retained earnings* [b]	—	—	(144)	—
Other	1	1	1	1
	(11)	(17)	(179)	(55)
Tax provision/(benefit) on other comprehensive income/(loss)	$ 62	$ (80)	$ 667	$ (218)

[a] Taxes are not provided for foreign currency translation adjustments relating to investments in international subsidiaries that will be held indefinitely.
[b] For additional information on the adoption of a new accounting standard related to reclassification of certain tax effects from AOCI, see *Note 1B.*
[c] For additional information on the adoption of a new accounting standard related to financial assets and liabilities, see *Note 1B* .

Note 6. Accumulated Other Comprehensive Loss, Excluding Noncontrolling Interests

The following table provides the changes, net of tax, in *Accumulated other comprehensive loss* :

	Net Unrealized Gains/(Losses)			Benefit Plans		
(MILLIONS OF DOLLARS)	Foreign Currency Translation Adjustments	Derivative Financial Instruments	Available-For-Sale Securities	Actuarial Gains/(Losses)	Prior Service (Costs)/Credits and Other	Accumulated Other Comprehensive Income/(Loss)
Balance, December 31, 2017	$ (5,180)	$ (30)	$ 401	$ (5,262)	$ 750	$ (9,321)
Other comprehensive income/(loss) due to the adoption of new accounting standards [a]	(2)	(1)	(416)	(637)	144	(913)
Other comprehensive income/(loss) [b]	(589)	279	(116)	361	(118)	(183)
Balance, September 30, 2018	$ (5,772)	$ 248	$ (131)	$ (5,538)	$ 776	$ (10,417)

[a] Amounts represent the cumulative effect adjustments as of January 1, 2018 from the adoption of new accounting standards related to (i) financial assets and liabilities and (ii) the reclassification of certain tax effects from AOCI. For additional information, see *Note 1B.*
[b] Amounts do not include foreign currency translation adjustments attributable to noncontrolling interests of $20 million loss for the first nine months of 2018 .

As of September 30, 2018 , with respect to derivative financial instruments, the amount of unrealized pre-tax net gains on derivative financial instruments estimated to be reclassified into income within the next 12 months is approximately $177 million , which is expected to be offset primarily by net losses resulting from reclassification adjustments related to net losses related to foreign currency exchange-denominated forecasted intercompany inventory sales and available-for-sale debt securities.

Note 7. Financial Instruments

A. Fair Value Measurements

Financial Assets and Liabilities Measured at Fair Value on a Recurring Basis

On January 1, 2018, we adopted a new accounting and disclosure standard related to accounting for the recognition of financial assets and liabilities. For additional information see *Note 1B* .

The following table presents the financial assets and liabilities measured at fair value using a market approach on a recurring basis by balance sheet categories and fair value hierarchy level as defined in Notes to Consolidated Financial Statements— *Note 1E. Basis of Presentation and Significant Accounting Policies: Fair Value* in Pfizer's 2017 Financial Report:

	September 30, 2018			December 31, 2017		
(MILLIONS OF DOLLARS)	Total	Level 1	Level 2	Total	Level 1	Level 2
Financial assets measured at fair value on a recurring basis:						
Short-term investments						
Classified as equity securities:						
Money market funds	$ 1,184	$ —	$ 1,184	$ 2,115	$ —	$ 2,115
Equity [(a)]	29	17	12	35	16	19
	1,213	17	1,196	2,150	16	2,134
Classified as available-for-sale debt securities:						
Government and agency—non-U.S.	8,336	—	8,336	12,242	—	12,242
Corporate	2,890	—	2,890	2,766	—	2,766
Government—U.S.	8	—	8	252	—	252
Agency asset-backed—U.S.	17	—	17	23	—	23
Other asset-backed	5	—	5	79	—	79
	11,256	—	11,256	15,362	—	15,362
Total short-term investments	12,469	17	12,452	17,512	16	17,496
Other current assets						
Derivative assets:						
Interest rate contracts	88	—	88	104	—	104
Foreign exchange contracts	488	—	488	234	—	234
Total other current assets	576	—	576	337	—	337
Long-term investments						
Classified as equity securities:						
Equity [(a)]	1,563	1,527	36	1,440	1,398	42
Classified as trading securities:						
Debt	50	50	—	73	73	—
	1,612	1,577	36	1,514	1,472	42
Classified as available-for-sale debt securities:						
Government and agency—non-U.S.	106	—	106	387	—	387
Corporate	3,210	—	3,210	4,172	36	4,136
Government—U.S.	421	—	421	495	—	495
Other asset-backed	4	—	4	35	—	35
	3,742	—	3,742	5,090	36	5,054
Total long-term investments	5,354	1,577	3,778	6,603	1,507	5,096
Other noncurrent assets						
Derivative assets:						
Interest rate contracts	246	—	246	477	—	477
Foreign exchange contracts	220	—	220	7	—	7
Total other noncurrent assets	467	—	467	484	—	484
Total assets	$ 18,866	$ 1,594	$ 17,272	$ 24,937	$ 1,523	$ 23,414
Financial liabilities measured at fair value on a recurring basis:						
Other current liabilities						
Derivative liabilities:						

Interest rate contracts	$ 5	$ —	$ 5	$ 1	$ —	$ 1
Foreign exchange contracts	80	—	80	201	—	201
Total other current liabilities	89	—	89	201	—	201
Other noncurrent liabilities						
Derivative liabilities:						
Interest rate contracts	653	—	653	177	—	177
Foreign exchange contracts	432	—	432	313	—	313
Total other noncurrent liabilities	1,085	—	1,085	490	—	490
Total liabilities	$ 1,174	$ —	$ 1,174	$ 691	$ —	$ 691

[(a)] As of September 30, 2018 , short-term equity securities of $12 million and long-term equity securities of $35 million are held in trust for benefits attributable to the former Pharmacia Savings Plus Plan. As of December 31, 2017 , short-term equity securities of $19 million and long-term equity securities of $42 million are held in trust for benefits attributable to the former Pharmacia Savings Plus Plan.

Financial Assets and Liabilities Not Measured at Fair Value on a Recurring Basis

The following table presents the financial liabilities not measured at fair value on a recurring basis, including the carrying values and estimated fair values:

	September 30, 2018			December 31, 2017		
	Carrying Value	Estimated Fair Value		Carrying Value	Estimated Fair Value	
(MILLIONS OF DOLLARS)		Total	Level 2		Total	Level 2
Financial Liabilities						
Long-term debt, excluding the current portion	$ 33,652	$ 36,243	$ 36,243	$ 33,538	$ 37,253	$ 37,253

The differences between the estimated fair values and carrying values of held-to-maturity debt securities, restricted stock and private equity securities at cost, and short-term borrowings not measured at fair value on a recurring basis were not significant as of September 30, 2018 or December 31, 2017 , except for our investment in Allogene (see *Note 2B*). The fair value measurements of our held-to-maturity debt securities and our short-term borrowings are based on Level 2 inputs. The fair value measurements of our private equity securities carried at cost, which represent investments in the life sciences sector, are based on Level 3 inputs.

In addition, as of September 30, 2018 and December 31, 2017 , we had long-term receivables whose fair value is based on Level 3 inputs. As of September 30, 2018 and December 31, 2017 , the differences between the estimated fair values and carrying values of these receivables were not significant.

Total Short-Term and Long-Term Investments

The following table represents our investments by classification type:

(MILLIONS OF DOLLARS)	September 30, 2018	December 31, 2017
Short-term investments		
Equity securities	$ 1,213	$ 2,150
Available-for-sale debt securities	11,256	15,362
Held-to-maturity debt securities	1,211	1,138
Total Short-term investments	$ 13,680	$ 18,650
Long-term investments		
Equity securities	$ 1,563	$ 1,440
Trading debt securities	50	73
Available-for-sale debt securities	3,742	5,090
Held-to-maturity debt securities	63	4
Private equity investments carried at equity-method or cost	1,027	408
Total Long-term investments	$ 6,444	$ 7,015
Held-to-maturity cash equivalents	$ 237	$ 719

Fair Value Methodology

The following inputs and valuation techniques were used to estimate the fair value of our financial assets and liabilities:

- Trading debt securities—quoted market prices.
- Available-for-sale debt securities—third-party matrix-pricing model that uses significant inputs derived from or corroborated by observable market data and credit-adjusted interest rate yield curves. Mortgage-backed, loan-backed and receivable-backed securities are valued by third-party models that use significant inputs derived from observable market data like prepayment rates, default rates, and recovery rates.
- Equity securities—quoted market prices.
- Derivative assets and liabilities (financial instruments)—third-party matrix-pricing model that uses significant inputs derived from or corroborated by observable market data. Where applicable, these models discount future cash flow amounts using market-based observable inputs, including interest rate yield curves, and forward and spot prices for currencies. The credit risk impact to our derivative financial instruments was not significant.
- Money market funds—observable net asset value prices.

We periodically review the methodologies, inputs and outputs of third-party pricing services for reasonableness. Our procedures can include, for example, referencing other third-party pricing models, monitoring key observable inputs (like LIBOR interest rates) and selectively performing test-comparisons of values with actual sales of financial instruments.

B. Investments

At September 30, 2018, the investment securities portfolio consisted of debt securities that were virtually all investment-grade. Information on investments in debt and equity securities at September 30, 2018 and December 31, 2017 is as follows, including, as of September 30, 2018, the contractual maturities, or as necessary, the estimated maturities, of the available-for-sale and held-to-maturity debt securities:

	September 30, 2018								December 31, 2017			
		Gross Unrealized			Maturities (in Years)					Gross Unrealized		
(MILLIONS OF DOLLARS)	Amortized Cost	Gains	Losses	Fair Value	Within 1	Over 1 to 5	Over 5	Total	Amortized Cost	Gains	Losses	Fair Value
Available-for-sale debt securities												
Government and agency — non-U.S.	$ 8,476	$ 9	$ (43)	$ 8,442	$ 8,336	$ 106	$ —	$ 8,442	$ 12,616	$ 61	$ (48)	$ 12,629
Corporate [a]	6,192	2	(94)	6,100	2,890	2,356	854	6,100	6,955	15	(33)	6,938
Government—U.S.	451	—	(23)	428	8	421	—	428	765	—	(19)	747
Agency asset-backed—U.S.	18	—	(1)	18	17	—	—	18	24	—	(1)	24
Other asset-backed [b]	9	—	—	9	5	3	2	9	114	—	—	114
Held-to-maturity debt securities												
Time deposits and other	734	—	—	734	670	23	40	734	1,091	—	—	1,091
Government and agency—non-U.S.	778	—	—	778	778	—	—	778	770	—	—	770
Total debt securities	$ 16,658	$ 11	$ (160)	$ 16,509	$ 12,704	$ 2,909	$ 896	$ 16,509	$ 22,337	$ 77	$ (100)	$ 22,313
Available-for-sale equity securities [c]												
Money market funds									$ 2,115	$ —	$ —	$ 2,115
Equity									728	586	(124)	1,190
Total available-for-sale equity securities									$ 2,843	$ 586	$ (124)	$ 3,304

[a] Issued by a diverse group of corporations.

[b] Includes mortgage-backed, loan-backed and receivable-backed securities , all of which are in senior positions in the capital structure of the security. Mortgage-backed securities are collateralized by diversified pools of residential and commercial mortgages. Loan-backed securities are collateralized by senior secured obligations of a diverse pool of companies or student loans. Receivable-backed securities are collateralized by credit cards receivables.

[c] Upon the 2018 adoption of a new accounting standard related to financial assets and liabilities, available-for-sale equity securities were classified as equity securities. For additional information see *Note 1B* .

The following table presents the net unrealized gains and losses for the period that relates to equity securities still held at the reporting date, calculated as follows:

(MILLIONS OF DOLLARS)	Three Months Ended September 30, 2018	Nine Months Ended September 30, 2018
Net gains recognized during the period on investments in equity securities [a]	$ 94	$ 460
Less: Net gains recognized during the period on equity securities sold during the period	(54)	(90)
Net unrealized gains during the reporting period on equity securities still held at the reporting date [b]	$ 40	$ 370

[a] The net gains on investments in equity securities are reported in *Other (income)/deductions — net* and, for the third quarter and first nine months of 2018 , include unrealized net gains on equity securities reflecting the adoption of a new accounting standard in the first quarter of 2018. For additional information, see *Note 4* .

[b] The third quarter of 2018 includes $8 million of unrealized net gains in *Other (income)/deductions — net* reflecting the adoption of a new accounting standard in the first quarter of 2018 and $32 million of unrealized gains on other equity securities. The first nine months of 2018 includes $344 million of unrealized net gains in *Other (income)/deductions — net* reflecting the adoption of a new accounting standard in the first quarter of 2018 and $26 million of unrealized gains on other equity securities. For additional information, see *Note 1B* and *Note 4* .

C. Short-Term Borrowings

Short-term borrowings include:

(MILLIONS OF DOLLARS)	September 30, 2018	December 31, 2017
Commercial paper	$ 2,600	$ 6,100
Current portion of long-term debt, principal amount	4,260	3,532
Other short-term borrowings, principal amount [(a)]	537	320
Total short-term borrowings, principal amount	7,396	9,951
Net fair value adjustments related to hedging and purchase accounting	(5)	14
Net unamortized discounts, premiums and debt issuance costs	(7)	(12)
Total *Short-term borrowings, including current portion of long-term debt* , carried at historical proceeds, as adjusted	$ 7,385	$ 9,953

[(a)] Other short-term borrowings primarily include cash collateral. For additional information, see *Note 7F* .

D. Long-Term Debt

New Issuances

In the third quarter of 2018, we issued the following senior unsecured notes:

(MILLIONS OF DOLLARS)	Maturity Date	Principal As of September 30, 2018
3.000% notes [(a)]	September 15, 2021	$ 1,000
Floating rate notes (LIBOR plus 0.33%) [(b)]	September 15, 2023	300
3.200% notes [(a)]	September 15, 2023	1,000
3.600% notes [(a)]	September 15, 2028	1,000
4.100% notes [(a)]	September 15, 2038	700
4.200% notes [(a)]	September 15, 2048	1,000
Total long-term debt issued in the third quarter of 2018		$ 5,000

[(a)] Fixed rate notes may be redeemed by us at any time, in whole, or in part, at varying redemption prices plus accrued and unpaid interest.
[(b)] Floating rate notes may not be redeemed by their terms prior to maturity.

The following table provides the aggregate principal amount of our senior unsecured long-term debt, and adjustments to report our aggregate long-term debt:

(MILLIONS OF DOLLARS)	September 30, 2018	December 31, 2017
Total long-term debt, principal amount	$ 33,658	$ 32,783
Net fair value adjustments related to hedging and purchase accounting	129	872
Net unamortized discounts, premiums and debt issuance costs	(142)	(125)
Other long-term debt	7	8
Total long-term debt, carried at historical proceeds, as adjusted	$ 33,652	$ 33,538
Current portion of long-term debt, carried at historical proceeds, as adjusted	$ 4,255	$ 3,546

E. Other Noncurrent Liabilities

Mylotarg (gemtuzumab ozogamicin)

In April 2018, the EU approved Mylotarg for the treatment of acute myeloid leukemia. In connection with the EU approval, we incurred an obligation to make guaranteed fixed annual payments over a ten -year period aggregating $301 million related to a research and development arrangement. We recorded the estimated net present value of $240 million as a liability and an intangible asset in *Developed technology rights* as of the approval date. In June 2018, we entered into a transaction with the obligee to buyout the remaining liability for the fixed annual payments for a lump sum payment of $224 million . As a result of the buyout transaction, the liability was extinguished and we recognized a non-cash $17 million pre-tax gain in *Other (income)/deductions—net* in the second quarter of 2018 (see *Note 4*).

Bosulif (bosutinib)

In December 2017, the U.S. FDA approved Bosulif for the treatment of patients with newly-diagnosed chronic-phase Ph+ CML. In connection with the U.S. approval, we incurred an obligation to make guaranteed fixed annual payments over a ten -

year period aggregating $416 million related to a research and development arrangement. We recorded the estimated net present value of $364 million as of the approval date as an intangible asset in *Developed technology rights* . In August 2018, we entered into a transaction with the obligee to buyout a portion of the remaining liability for the fixed annual payments for a lump sum payment of $71 million . As a result of the buyout transaction, the liability was reduced and we recognized a non-cash $9 million pre-tax gain in *Other (income)/deductions—net* in the third quarter of 2018 . The present value of the remaining future payments as of September 30, 2018 is $208 million , of which $23 million is recorded in *Other current liabilities* and $185 million is recorded in *Other noncurrent liabilities* .

Besponsa (inotuzumab ozogamicin)

In August 2017, the U.S. FDA approved Besponsa and in June 2017, the EU approved Besponsa as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia. In connection with the U.S. approval, we incurred an obligation to make guaranteed fixed annual payments over a nine -year period aggregating $296 million related to a research and development arrangement. We recorded the estimated net present value of $248 million as of the approval date as an intangible asset in *Developed technology rights* . The present value of the remaining future payments as of September 30, 2018 is $240 million , of which $7 million is recorded in *Other current liabilities* and $233 million is recorded in *Other noncurrent liabilities* . In connection with the EU approval, we incurred an obligation to make guaranteed fixed annual payments over a nine -year period aggregating $148 million related to a research and development arrangement. We recorded the estimated net present value of $123 million as of the approval date as an intangible asset in *Developed technology rights* . The present value of the remaining future payments as of September 30, 2018 is $121 million , of which $3 million is recorded in *Other current liabilities* and $118 million is recorded in *Other noncurrent liabilities* .

The differences between the estimated fair values in the Level 2 fair value hierarchy and carrying values of these obligations were not significant as of September 30, 2018 .

F. Derivative Financial Instruments and Hedging Activities

We adopted a new accounting standard in the first quarter of 2018, as of January 2018. For additional information, see *Note 1B.*

Foreign Exchange Risk

A significant portion of our revenues, earnings and net investments in foreign affiliates is exposed to changes in foreign exchange rates. We manage our foreign exchange risk, in part, through operational means, including managing same-currency revenues in relation to same-currency costs and same-currency assets in relation to same-currency liabilities. We also manage our foreign exchange risk, depending on market conditions, through fair value, cash flow, and net investment hedging programs through the use of derivative financial instruments and foreign currency debt. These financial instruments serve to protect net income against the impact of remeasurement into another currency, or against the impact of translation into U.S. dollars of certain foreign exchange-denominated transactions.

All derivative financial instruments used to manage foreign currency risk are measured at fair value and are reported as assets or liabilities on the consolidated balance sheet. The derivative financial instruments primarily hedge or offset exposures in the euro, Japanese yen, U.K. pound and Swedish krona . Changes in fair value are reported in earnings or in *Other comprehensive income/(loss)* , depending on the nature and purpose of the financial instrument (hedge or offset relationship) and the effectiveness of the hedge relationships, as follows:

- Generally, we recognize the gains and losses on foreign exchange contracts that are designated as fair value hedges in earnings upon the recognition of the change in fair value of the hedged risk. Upon the adoption of the new standard in 2018, for certain foreign exchange contracts, we exclude an amount from the assessment of hedge effectiveness and recognize that excluded amount through an amortization approach. We also recognize the offsetting foreign exchange impact attributable to the hedged item in earnings.
- Generally, we record in *Other comprehensive income/(loss)* gains or losses on foreign exchange contracts that are designated as cash flow hedges and reclassify those amounts, as appropriate, into earnings in the same period or periods during which the hedged transaction affects earnings. Upon the adoption of the new standard in 2018, for certain foreign exchange contracts, we exclude an amount from the assessment of hedge effectiveness and recognize that excluded amount through an amortization approach.
- Historically, as part of our net investment hedging program, we recognize the gain and loss impact on foreign exchange contracts designated as hedges of our net investments in earnings in three ways: over time — for the periodic net swap payments; immediately — to the extent of any change in the difference between the foreign exchange spot rate and forward rate; and upon sale or substantial liquidation of our net investments — to the extent of change in the foreign exchange spot rates. Upon the adoption of the new standard in 2018, for foreign exchange contracts, we exclude an amount from the

assessment of hedge effectiveness and recognize that excluded amount through an amortization approach. We record in *Other comprehensive income/(loss)* the foreign exchange gains and losses related to foreign exchange-denominated debt designated as a hedge of our net investments in foreign subsidiaries and reclassify those amounts into earnings upon the sale or substantial liquidation of our net investments.

- For certain foreign exchange contracts not designated as hedging instruments, we recognize the gains and losses on foreign currency exchange contracts that are used to offset the same foreign currency assets or liabilities immediately into earnings along with the earnings impact of the items they generally offset. These contracts essentially take the opposite currency position of that reflected in the month-end balance sheet to counterbalance the effect of any currency movement.

As a part of our cash flow hedging program, we designate foreign exchange contracts to hedge a portion of our forecasted euro, Japanese yen, Chinese renminbi, Canadian dollar, U.K. pound, and Australian dollar -denominated intercompany inventory sales expected to occur no more than two years from the date of each hedge.

For the third quarter and first nine months ended October 1, 2017 , any ineffectiveness is recognized immediately into earnings. There is no significant ineffectiveness for these periods.

Interest Rate Risk

Our interest-bearing investments and borrowings are subject to interest rate risk. With respect to our investments, we strive to maintain a predominantly floating-rate basis position, but our strategy may change based on prevailing market conditions. We currently borrow primarily on a long-term, fixed rate basis. Historically, we strove to borrow primarily on a floating-rate basis; but in recent years we borrowed on a long-term, fixed-rate basis. From time to time, depending on market conditions, we will change the profile of our outstanding debt by entering into derivative financial instruments like interest rate swaps. We entered into derivative financial instruments to hedge or offset the fixed interest rates on the hedged item, matching the amount and timing of the hedged item. The derivative financial instruments primarily hedge U.S. dollar fixed-rate debt.

All derivative contracts used to manage interest rate risk are measured at fair value and reported as assets or liabilities on the consolidated balance sheet. Changes in fair value are reported in earnings, as follows:

- We recognize the gains and losses on interest rate contracts that are designated as fair value hedges in earnings upon the recognition of the change in fair value of the hedged risk. We also recognize the offsetting earnings impact of fixed-rate debt attributable to the hedged risk in earnings.

For the third quarter and first nine months ended October 1, 2017 , any ineffectiveness is recognized immediately into earnings. There is no significant ineffectiveness for these periods.

The following table provides the fair value of the derivative financial instruments and the related notional amounts presented between those derivatives that are designated as hedging instruments and those that are not designated as hedging instruments:

(MILLIONS OF DOLLARS)	September 30, 2018			December 31, 2017		
		Fair Value			Fair Value	
	Notional	Asset	Liability	Notional	Asset	Liability
Derivatives designated as hedging instruments:						
Foreign exchange contracts [(a)]	$ 19,955	$ 590	$ 464	$ 18,723	$ 179	$ 459
Interest rate contracts	11,300	335	661	12,430	581	178
		925	1,126		760	637
Derivatives not designated as hedging instruments:						
Foreign exchange contracts	$ 16,798	118	48	$ 14,300	62	54
Total		$ 1,043	$ 1,174		$ 822	$ 691

[(a)] As of September 30, 2018 , the notional amount of outstanding foreign currency forward-exchange contracts hedging our intercompany forecasted inventory sales was $5.4 billion .

The following table provides information about the gains/(losses) incurred to hedge or offset operational foreign exchange or interest rate risk:

(MILLIONS OF DOLLARS)	Amount of Gains/(Losses) Recognized in OID [a], [b]		Amount of Gains/(Losses) Recognized in OCI [a], [c]		Amount of Gains/(Losses) Reclassified from OCI into OID and COS [a], [c]	
	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017
Three Months Ended						
Derivative Financial Instruments in Cash Flow Hedge Relationships:						
Foreign exchange contracts [d]	$ —	$ 1	$ 183	$ (51)	$ 198	$ (56)
Amount excluded from effectiveness testing recognized in earnings based on an amortization approach	—	—	39	—	36	—
Derivative Financial Instruments in Fair Value Hedge Relationships:						
Interest rate contracts	(195)	10	—	—	—	—
Hedged item gain/(loss)	195	(10)	—	—	—	—
Foreign exchange contracts	1	(11)	—	—	—	—
Hedged item gain/(loss)	(1)	11	—	—	—	—
Derivative Financial Instruments in Net Investment Hedge Relationships:						
Foreign exchange contracts	—	—	43	—	—	—
The portion of gains/(losses) on foreign exchange contracts excluded from the assessment of hedge effectiveness	—	—	14	—	21	—
Non-Derivative Financial Instruments in Net Investment Hedge Relationships:						
Foreign currency short-term borrowings [e]	—	—	8	—	—	—
Foreign currency long-term debt [e]	—	—	17	(166)	—	—
Derivative Financial Instruments Not Designated as Hedges:						
Foreign exchange contracts	150	33	—	—	—	—
All other net	—	—	—	1	—	—
	$ 150	$ 34	$ 304	$ (216)	$ 256	$ (55)

(MILLIONS OF DOLLARS)	Amount of Gains/(Losses) Recognized in OID [a], [b]		Amount of Gains/(Losses) Recognized in OCI [a], [c]		Amount of Gains/(Losses) Reclassified from OCI into OID and COS [a], [c]	
	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017
Nine Months Ended						
Derivative Financial Instruments in Cash Flow Hedge Relationships:						
Foreign exchange contracts [d]	$ —	$ (5)	$ 147	$ (149)	$ (204)	$ 394
Amount excluded from effectiveness testing recognized in earnings based on an amortization approach	—	—	87	—	84	—
Derivative Financial Instruments in Fair Value Hedge Relationships:						
Interest rate contracts	(715)	19	—	—	—	—
Hedged item gain/(loss)	715	(19)	—	—	—	—
Foreign exchange contracts	5	(19)	—	—	—	—
Hedged item gain/(loss)	(5)	19	—	—	—	—
Derivative Financial Instruments in Net Investment Hedge Relationships:						
Foreign exchange contracts	—	—	191	—	—	—
The portion of gains/(losses) on foreign exchange contracts excluded from the assessment of hedge effectiveness	—	—	41	—	47	—
Non-Derivative Financial Instruments in Net Investment Hedge Relationships:						
Foreign currency short-term borrowings [e]	—	—	50	—	—	—
Foreign currency long-term debt [e]	—	—	111	(518)	—	—
Derivative Financial Instruments Not Designated as Hedges:						
Foreign exchange contracts	156	(112)	—	—	—	—
All other net	—	—	1	1	1	—
	$ 156	$ (117)	$ 629	$ (666)	$ (72)	$ 394

[a] OID = Other (income)/deductions—net, included in *Other (income)/deductions—net* in the condensed consolidated statements of income . COS = Cost of Sales, included in *Cost of sales* in the condensed consolidated statements of income. OCI = Other comprehensive income/(loss), included in the condensed consolidated statements of comprehensive income .

[b] For the third quarter and first nine months ended October 1, 2017 , there was no significant ineffectiveness.

[c] For derivative financial instruments in cash flow hedge relationships, the gains and losses are included in *Other comprehensive income/(loss)— Unrealized holding gains/(losses) on derivative financial instruments, net* . For derivative financial instruments in net investment hedge relationships and for foreign currency debt designated as hedging instruments, the effective portion is included in *Other comprehensive income/(loss)—Foreign currency translation adjustments, net.*

[d] Based on quarter-end foreign exchange rates that are subject to change, we expect to reclassify a pre-tax gain of $120 million within the next 12 months into *Cost of sales*. The maximum length of time over which we are hedging future foreign exchange cash flow relates to our $1.8 billion U.K. pound debt maturing in 2043.

[e] Short-term borrowings include foreign currency short-term borrowings with carrying values of $1.5 billion as of September 30, 2018 , which are used as hedging instruments in net investment hedges. Long-term debt includes foreign currency long-term borrowings with carrying values of $3.2 billion as of September 30, 2018 , which are used as hedging instruments in net investment hedges.

The following table provides the total amount of each income and expense line in which the results of fair value or cash flow hedges are recorded:

(MILLIONS OF DOLLARS)	Three Months Ended September 30, 2018	Nine Months Ended September 30, 2018
Cost of sales	$ 2,694	$ 8,173
Other (income)/deductions—net	(414)	(1,143)

The following table provides the amounts recorded in our condensed consolidated balance sheet related to cumulative basis adjustments for fair value hedges:

(MILLIONS OF DOLLARS)	Carrying Amount of Hedged Assets/Liabilities September 30, 2018	Cumulative Amount of Fair Value Hedging Adjustment Gains/(Losses) Included in the Carrying Amount of the Hedged Assets/Liabilities September 30, 2018
Short-term investments	$ 156	$ —
Long-term investments	45	(1)
Short-term borrowings, including current portion of long-term debt	1,490	8
Long-term debt	9,548	407

Certain of our derivative instruments are covered by associated credit-support agreements that have credit-risk-related contingent features designed to reduce both counterparties' exposure to risk of defaulting on amounts owed by the other party. As of September 30, 2018 , the aggregate fair value of these derivative instruments that are in a net liability position was $545 million , for which we have posted collateral of $535 million in the normal course of business. If there had been a downgrade to below an A rating by S&P or the equivalent rating by Moody's, we would not have been required to post any additional collateral to our counterparties.

As of September 30, 2018 , we received cash collateral of $472 million from various counterparties. The collateral primarily supports the approximate fair value of our derivative contracts. With respect to the collateral received, the obligations are reported in *Short-term borrowings, including current portion of long-term debt.*

G. Credit Risk

On an ongoing basis, we review the creditworthiness of counterparties to our foreign exchange and interest rate agreements and do not expect to incur a significant loss from failure of any counterparties to perform under the agreements. There are no significant concentrations of credit risk related to our financial instruments with any individual counterparty, except for certain significant customers. For additional information as to significant customers, see Notes to Consolidated Financial Statements— *Note 18C. Segment, Geographic and Other Revenue Information: Other Revenue Information* in Pfizer's 2017 Financial Report. As of September 30, 2018 , we had amounts due from a well-diversified, high quality group of banks ($2.1 billion) from around the world. For details about our investments, see *Note 7B* above .

In general, there is no requirement for collateral from customers. However, derivative financial instruments are executed under credit-support agreements that provide for the ability to request to receive cash collateral, depending on levels of exposure, our credit rating and the credit rating of the counterparty, see *Note 7F* above.

Note 8. Inventories

The following table provides the components of *Inventories* :

(MILLIONS OF DOLLARS)	September 30, 2018	December 31, 2017
Finished goods	$ 2,581	$ 2,883
Work-in-process	4,764	3,908
Raw materials and supplies	839	788
Inventories [(a)]	$ 8,184	$ 7,578
Noncurrent inventories not included above [(b)]	$ 576	$ 683

[(a)] The change from December 31, 2017 reflects increases for certain products to meet targeted levels in the normal course of business, including inventory build for supply recovery, network strategy and new product launches, partially offset by a decrease due to foreign exchange.
[(b)] Included in *Other noncurrent assets* . There are no recoverability issues associated with these amounts.

Note 9. Identifiable Intangible Assets and Goodwill

A. Identifiable Intangible Assets

Balance Sheet Information

The following table provides the components of *Identifiable intangible assets* :

(MILLIONS OF DOLLARS)	September 30, 2018 Gross Carrying Amount	Accumulated Amortization	Identifiable Intangible Assets, less Accumulated Amortization	December 31, 2017 Gross Carrying Amount	Accumulated Amortization	Identifiable Intangible Assets, less Accumulated Amortization
Finite-lived intangible assets						
Developed technology rights [a]	$ 92,123	$ (57,786)	$ 34,337	$ 89,550	$ (54,785)	$ 34,765
Brands	2,126	(1,228)	898	2,134	(1,152)	982
Licensing agreements and other	1,938	(1,160)	777	1,911	(1,096)	815
	96,187	(60,175)	36,012	93,595	(57,033)	36,562
Indefinite-lived intangible assets						
Brands and other	6,909		6,909	6,929		6,929
IPR&D [a]	2,385		2,385	5,249		5,249
	9,294		9,294	12,179		12,179
Identifiable intangible assets [b]	$ 105,481	$ (60,175)	$ 45,306	$ 105,774	$ (57,033)	$ 48,741

[a] The changes in the gross carrying amount of *Developed technology rights* and *IPR&D* primarily reflect (i) the transfer of $2.7 billion from *IPR&D* to *Developed technology rights* to reflect the approval of Xtandi in the U.S. for the treatment of men with non-metastatic castration-resistant prostate cancer, which is being developed through a collaboration with Astellas, and (ii) $240 million of *Developed technology rights* recorded in connection with the EU approval of Mylotarg (see *Note 7E*).

[b] The decrease in *I dentifiable intangible assets, less accumulated amortization* , is primarily due to amortization, partially offset by additions, mainly consisting of $240 million of *Developed technology rights* recorded in connection with the EU approval of Mylotarg (see *Note 7E*).

Our identifiable intangible assets are associated with the following, as a percentage of total identifiable intangible assets, less accumulated amortization:

	September 30, 2018 IH	EH	WRD
Developed technology rights	70%	29%	—
Brands, finite-lived	75%	25%	—
Brands, indefinite-lived	71%	29%	—
IPR&D	64%	21%	15%

Amortization

Total amortization expense for finite-lived intangible assets was $1.3 billion for the third quarter of 2018 and $1.2 billion for the third quarter of 2017 , and $3.7 billion for the first nine months of 2018 and $3.6 billion for the first nine months of 2017 .

B. Goodwill

The following table provides the components of and changes in the carrying amount of *Goodwill* :

(MILLIONS OF DOLLARS)	IH	EH	Total
Balance, December 31, 2017	$ 31,141	$ 24,811	$ 55,952
Other [a]	(178)	(160)	(338)
Balance, September 30, 2018	$ 30,964	$ 24,651	$ 55,614

[a] Primarily reflects the impact of foreign exchange, as well as the contribution of the allogeneic CAR T developmental program assets and operations to Allogene that constituted a business for accounting purposes (see *Note 2B*).

Note 10. Pension and Postretirement Benefit Plans

The following table provides the components of net periodic benefit cost/(credit):

	Three Months Ended							
	Pension Plans							
	U.S. Qualified [a]		U.S. Supplemental (Non-Qualified)		International		Postretirement Plans	
(MILLIONS OF DOLLARS)	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017
Net periodic benefit cost/(credit) [b] :								
Service cost [c]	$ —	$ 67	$ —	$ 6	$ 33	$ 44	$ 10	$ 10
Interest cost	149	157	14	13	52	52	18	23
Expected return on plan assets	(259)	(248)	—	—	(89)	(87)	(9)	(9)
Amortization of:								
Actuarial losses [c]	30	91	3	12	25	29	2	8
Prior service credits	—	—	—	—	(1)	(1)	(45)	(45)
Curtailments	1	1	1	—	(4)	(2)	(1)	(3)
Settlements	38	30	3	7	—	—	—	—
	$ (40)	$ 99	$ 20	$ 39	$ 17	$ 35	$ (26)	$ (17)

	Nine Months Ended							
	Pension Plans							
	U.S. Qualified [a]		U.S. Supplemental (Non-Qualified)		International		Postretirement Plans	
(MILLIONS OF DOLLARS)	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017
Net periodic benefit cost/(credit) [b] :								
Service cost [c]	$ —	$ 202	$ —	$ 18	$ 104	$ 127	$ 29	$ 32
Interest cost	450	478	40	41	160	152	54	68
Expected return on plan assets	(783)	(759)	—	—	(274)	(256)	(28)	(27)
Amortization of:								
Actuarial losses [c]	90	302	10	37	77	86	5	23
Prior service costs/(credits)	1	3	(1)	(1)	(3)	(3)	(135)	(137)
Curtailments	11	10	1	—	(4)	(2)	(15)	(15)
Settlements	84	54	24	32	—	3	—	—
	$ (147)	$ 292	$ 75	$ 127	$ 61	$ 106	$ (89)	$ (57)

[a] In the second quarter of 2017, we settled the remaining obligation associated with the Hospira U.S. qualified defined benefit pension plan. We purchased a group annuity contract on behalf of the remaining plan participants with a third-party insurance provider. As a result, we were relieved of the $156 million net pension benefit obligation and recorded a pre-tax settlement gain of $41 million , partially offset by the recognition of actuarial losses and prior service costs upon plan settlement of approximately $30 million in *Other (income)/deductions—net* (see *Note 3*).

[b] We adopted a new accounting standard on January 1, 2018 that requires the net periodic pension and postretirement benefit costs other than service costs be presented in *Other (income)/deductions—net* on the condensed consolidated statements of income. For additional information, see *Note 1B* and *Note 4* .

[c] Effective January 1, 2018, we froze two significant defined benefit pension plans to future benefit accruals in the U.S. and U.K. and as a result, service costs for those plans are eliminated. In addition, due to the plan freeze, the average amortization period for the U.S. qualified plans and U.S. supplemental (non-qualified) plans was extended to the expected life expectancy of the plan participants, whereas the average amortization period in prior years utilized the expected future service period of plan participants.

The following table provides the amounts we contributed, and the amounts we expect to contribute during 2018, to our pension and postretirement plans from our general assets for the periods indicated:

	Pension Plans			
(MILLIONS OF DOLLARS)	U.S. Qualified	U.S. Supplemental (Non-Qualified)	International	Postretirement Plans
Contributions from our general assets for the nine months ended September 30, 2018	$ 500	$ 118	$ 174	$ 108
Expected contributions from our general assets during 2018 [a]	500	137	229	149

[a] Contributions expected to be made for 2018 are inclusive of amounts contributed during the nine months ended September 30, 2018 , including the $500 million voluntary contribution that was made in February 2018 for the U.S. qualified plans, which was considered pre-funding for future anticipated mandatory contributions and is also expected to reduce Pension Benefit Guaranty Corporation variable rate premiums. The U.S. supplemental (non-qualified) pension plan, international pension plan and the postretirement plan contributions from our general assets include direct employer benefit payments.

Note 11. Earnings Per Common Share Attributable to Common Shareholders

The following table provides the detailed calculation of *EPS* :

	Three Months Ended		Nine Months Ended	
(IN MILLIONS)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
EPS Numerator—Basic				
Income from continuing operations	$ 4,111	$ 2,858	$ 11,562	$ 9,064
Less: Net income attributable to noncontrolling interests	8	18	25	32
Income from continuing operations attributable to Pfizer Inc.	4,103	2,840	11,537	9,032
Less: Preferred stock dividends—net of tax	—	—	1	1
Income from continuing operations attributable to Pfizer Inc. common shareholders	4,103	2,839	11,536	9,032
Discontinued operations—net of tax	11	—	10	1
Net income attributable to Pfizer Inc. common shareholders	$ 4,114	$ 2,839	$ 11,546	$ 9,033
EPS Numerator—Diluted				
Income from continuing operations attributable to Pfizer Inc. common shareholders and assumed conversions	$ 4,103	$ 2,840	$ 11,537	$ 9,032
Discontinued operations—net of tax, attributable to Pfizer Inc. common shareholders and assumed conversions	11	—	10	1
Net income attributable to Pfizer Inc. common shareholders and assumed conversions	$ 4,114	$ 2,840	$ 11,546	$ 9,034
EPS Denominator				
Weighted-average number of common shares outstanding—Basic	5,875	5,951	5,899	5,972
Common-share equivalents: stock options, stock issuable under employee compensation plans, convertible preferred stock and accelerated share repurchase agreements	112	89	99	85
Weighted-average number of common shares outstanding—Diluted	5,986	6,041	5,998	6,057
Stock options that had exercise prices greater than the average market price of our common stock issuable under employee compensation plans [a]	5	47	3	47

[a] These common stock equivalents were outstanding for the periods presented, but were not included in the computation of diluted EPS for those periods because their inclusion would have had an anti-dilutive effect.

Note 12. Contingencies and Certain Commitments

We and certain of our subsidiaries are subject to numerous contingencies arising in the ordinary course of business, including tax and legal contingencies. For a discussion of our tax contingencies, see *Note 5C.* For a discussion of our legal contingencies, see below.

A. Legal Proceedings

Our legal contingencies include, but are not limited to, the following:

- Patent litigation, which typically involves challenges to the coverage and/or validity of patents on various products, processes or dosage forms. We are the plaintiff in the majority of these actions. An adverse outcome in actions in which we are the plaintiff could result in loss of patent protection for a drug, a significant loss of revenues from that drug or impairment of the value of associated assets.
- Product liability and other product-related litigation, which can include personal injury, consumer, off-label promotion, securities, antitrust and breach of contract claims, among others, often involves highly complex issues relating to medical causation, label warnings and reliance on those warnings, scientific evidence and findings, actual, provable injury and other matters.
- Commercial and other matters, which can include merger-related and product-pricing claims and environmental claims and proceedings, can involve complexities that will vary from matter to matter.
- Government investigations, which often are related to the extensive regulation of pharmaceutical companies by national, state and local government agencies in the U.S. and in other jurisdictions.

Certain of these contingencies could result in losses, including damages, fines and/or civil penalties, which could be substantial, and/or criminal charges.

We believe that our claims and defenses in matters in which we are a defendant are substantial, but litigation is inherently unpredictable and excessive verdicts do occur. We do not believe that any of these matters will have a material adverse effect on our financial position. However, we could incur judgments, enter into settlements or revise our expectations regarding the outcome of certain matters, and such developments could have a material adverse effect on our results of operations in the period in which the amounts are accrued and/or our cash flows in the period in which the amounts are paid.

We have accrued for losses that are both probable and reasonably estimable. Substantially all of our contingencies are subject to significant uncertainties and, therefore, determining the likelihood of a loss and/or the measurement of any loss can be complex. Consequently, we are unable to estimate the range of reasonably possible loss in excess of amounts accrued. Our assessments are based on estimates and assumptions that have been deemed reasonable by management, but the assessment process relies heavily on estimates and assumptions that may prove to be incomplete or inaccurate, and unanticipated events and circumstances may occur that might cause us to change those estimates and assumptions.

Amounts recorded for legal and environmental contingencies result from a complex series of judgments about future events and uncertainties and rely heavily on estimates and assumptions.

The principal pending matters to which we are a party are discussed below. In determining whether a pending matter is a principal matter, we consider both quantitative and qualitative factors in order to assess materiality, such as, among other things, the amount of damages and the nature of any other relief sought in the proceeding, if such damages and other relief are specified; our view of the merits of the claims and of the strength of our defenses; whether the action purports to be, or is, a class action and, if not certified, our view of the likelihood that a class will be certified by the court; the jurisdiction in which the proceeding is pending; whether related actions have been transferred to multidistrict litigation; any experience that we or, to our knowledge, other companies have had in similar proceedings; whether disclosure of the action would be important to a reader of our financial statements, including whether disclosure might change a reader's judgment about our financial statements in light of all of the information that is available to the reader; the potential impact of the proceeding on our reputation; and the extent of public interest in the matter. In addition, with respect to patent matters in which we are the plaintiff, we consider, among other things, the financial significance of the product protected by the patent(s) at issue. As a result of considering qualitative factors in our determination of principal matters, there are some matters discussed below with respect to which management believes that the likelihood of possible loss in excess of amounts accrued is remote.

A1. Legal Proceedings—Patent Litigation

Like other pharmaceutical companies, we are involved in numerous suits relating to our patents, including but not limited to, those discussed below. Most of the suits involve claims by generic drug manufacturers that patents covering our products, processes or dosage forms are invalid and/or do not cover the product of the generic drug manufacturer. Also, counterclaims, as well as various independent actions, have been filed alleging that our assertions of, or attempts to enforce, patent rights with respect to certain products constitute unfair competition and/or violations of antitrust laws. In addition to the challenges to the U.S. patents on a number of our products that are discussed below, patent rights to certain of our products are being challenged in various other jurisdictions. We are also party to patent damages suits in various jurisdictions pursuant to which generic drug manufacturers, payers, governments or other parties are seeking damages from us for allegedly causing delay of generic entry. Additionally, our licensing and collaboration partners face challenges by generic drug manufacturers to patents covering products for which we have licenses or co-promotion rights. We also are often involved in other proceedings, such as inter partes review, post-grant review, re-examination or opposition proceedings, before the U.S. Patent and Trademark Office, the European Patent Office, or other foreign counterparts relating to our intellectual property or the intellectual property rights of others. Also, if one of our patents is found to be invalid by such proceedings, generic or competitive products could be introduced into the market resulting in the erosion of sales of our existing products. For example, several of the patents in our pneumococcal vaccine portfolio were challenged in inter partes review and post-grant review proceedings in the United States. In June 2018, the Patent Trial and Appeal Board ruled on one patent, holding that one claim was valid and that all other claims were invalid. The party challenging that patent has appealed the decision. Challenges to other patents remain pending before the U.S. Patent and Trademark Office. The invalidation of these patents could potentially allow a competitor pneumococcal vaccine into the marketplace. We are also subject to patent litigation pursuant to which one or more third parties seeks damages and/or injunctive relief to compensate for alleged infringement of its patents by our commercial or other activities. For example, our Hospira subsidiaries are involved in patent and patent-related disputes over their attempts to bring generic pharmaceutical and biosimilar products to market. If one of our marketed products is found to infringe valid patent rights of a third party, such third party may be awarded significant damages, or we may be prevented from further sales of that product. Such damages may be enhanced as much as three-fold in the event that we or one of our subsidiaries, like Hospira, is found to have willfully infringed valid patent rights of a third party.

Actions In Which We Are The Plaintiff

Bosulif (bosutinib)
In December 2016, Wyeth LLC, Wyeth Pharmaceuticals Inc., and PF Prism C.V. (collectively, Wyeth) brought a patent-infringement action against Alembic Pharmaceuticals, Ltd, Alembic Pharmaceuticals, Inc. (collectively, Alembic), Sun Pharmaceutical Industries, Inc., and Sun Pharmaceutical Industries Limited (collectively, Sun), in the U.S. District Court for the District of Delaware in connection with abbreviated new drug applications respectively filed with the FDA by Alembic and Sun, each seeking approval to market generic versions of bosutinib. Alembic is challenging patents, which expire in 2026, covering polymorphic forms of bosutinib and methods of treating chronic myelogenous leukemia. Sun is challenging the patent covering polymorphic forms of bosutinib that expires in 2026. In March 2017, Wyeth brought a patent-infringement action against MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc. (collectively, MSN), in the U.S. District Court for the District of Delaware in connection with an abbreviated new drug application filed with the FDA by MSN, seeking approval to market a generic version of bosutinib, and challenging a patent expiring in 2026 covering polymorphic forms of bosutinib. In September 2017, the case against MSN was dismissed. Also, in September 2017, Wyeth brought an additional patent-infringement action against Sun in the U.S. District Court for the District of Delaware asserting the infringement and validity of two other patents challenged by Sun, which expire in 2025 and 2026, respectively, covering compositions of bosutinib and methods of treating chronic myelogenous leukemia.

EpiPen
In July 2010, King, which we acquired in 2011 and is a wholly-owned subsidiary, brought a patent-infringement action against Sandoz in the U.S. District Court for the District of New Jersey in connection with Sandoz's abbreviated new drug application filed with the FDA seeking approval to market an epinephrine injectable product. Sandoz is challenging patents, which expire in 2025, covering the next-generation autoinjector for use with epinephrine that is sold under the EpiPen brand name.

Precedex Premix
In June 2014, Ben Venue Laboratories, Inc. (Ben Venue) notified our subsidiary, Hospira, that it had filed an abbreviated new drug application with the FDA seeking approval to market a generic version of Hospira's premix version of Precedex and containing allegations that a patent relating to the use of Precedex in an intensive care unit setting, which expires in March 2019, was invalid or not infringed. In August 2014, Hospira and Orion Corporation (co-owner of the patent that is the subject of the lawsuit) filed suit against Ben Venue, Hikma Pharmaceuticals PLC (Hikma), and West-Ward Pharmaceutical Corp. in the U.S. District Court for the District of Delaware asserting the validity and infringement of the patent. In October 2014,

Eurohealth International Sarl was substituted for Ben Venue and Hikma. In June 2016, this case was settled on terms not material to Pfizer.

In June 2015, Amneal Pharmaceuticals LLC (Amneal) notified Hospira that it had filed an abbreviated new drug application with the FDA seeking approval to market a generic version of Hospira's premix version of Precedex and containing allegations that four patents relating to the Precedex premix formulations and their use, all of which expire in 2032, were invalid or not infringed. In August 2015, Hospira filed suit against Amneal in the U.S. District Court for the District of Delaware asserting the validity and infringement of the patents that are the subject of the lawsuit. In January 2018, the District Court ruled that one of the four patents was valid and infringed, and that the other three patents were invalid. In February and March 2018, respectively, each of Amneal and Hospira appealed the District Court decision to the U.S. Court of Appeals for the Federal Circuit.

In December 2015, Fresenius Kabi USA LLC (Fresenius) notified Hospira that it had filed an abbreviated new drug application with the FDA seeking approval to market a generic version of Hospira's premix version of Precedex and containing allegations that four patents relating to the Precedex premix formulations and their use, all of which expire in 2032, were invalid or not infringed. In January 2016, Hospira filed suit against Fresenius in the U.S. District Court for the Northern District of Illinois asserting the validity and infringement of the patents that are the subject of the lawsuit.

In August 2016, Par Sterile Products, LLC (Par) notified Hospira that it had filed an abbreviated new drug application with the FDA seeking approval to market a generic version of Hospira's premix version of Precedex and containing allegations that four patents relating to the Precedex premix formulations and their use, all of which expire in 2032, were invalid or not infringed. In September 2016, Hospira filed suit against Par in the U.S. District Court for the District of Delaware asserting the validity and infringement of the patents that are the subject of the lawsuit. In December 2016, the case was stayed pending the outcome of Hospira's suit against Amneal (including all appeals).

In December 2017, Gland Pharma Limited (Gland) notified Hospira that it had filed an abbreviated new drug application with the FDA seeking approval to market a generic version of Hospira's premix version of Precedex and containing allegations that six patents relating to the Precedex premix formulations and their use, all of which expire in 2032, were invalid or not infringed. In February 2018, Hospira filed suit against Gland in the U.S. District Court for the District of Delaware asserting the validity and infringement of four patents that are the subject of the lawsuit.

In December 2017, Jiangsu Hengrui Medicine Co., Ltd. (Hengrui) notified Hospira that it had filed an abbreviated new drug application with the FDA seeking approval to market a generic version of Hospira's premix version of Precedex and containing allegations that six patents relating to the Precedex premix formulations and their use, all of which expire in 2032, were invalid or not infringed. In February 2018, Hospira filed suit against Hengrui in the U.S. District Court for the District of Delaware asserting the validity and infringement of four patents that are the subject of the lawsuit.

In February 2018, Baxter Healthcare Corporation (Baxter) filed a declaratory judgment action against Hospira in the U.S. District Court for the District of Delaware seeking a declaration of non-infringement of four patents relating to the Precedex premix formulations and their use. One of the patents included in the action expires in 2019 and the other three patents expire in 2032. In March 2018, Hospira filed a counterclaim for infringement of the patent expiring in 2019.

Xeljanz (tofacitinib)

In February 2017, we brought a patent-infringement action against MicroLabs USA Inc. and MicroLabs Ltd. (collectively, MicroLabs) in the U.S. District Court for the District of Delaware asserting the infringement and validity of three patents challenged by MicroLabs in its abbreviated new drug application seeking approval to market a generic version of tofacitinib 5 mg tablets. Of the three patents that are the subject of the lawsuit, one covers the active ingredient and expires in December 2025, the second covers an enantiomer of tofacitinib and expires in 2022, and the third covers a polymorphic form of tofacitinib and expires in 2023. Three other patents for Xeljanz expiring in December 2020 have not been challenged by MicroLabs.

Separately, also in February 2017, we brought a patent-infringement action against Sun Pharmaceutical Industries Ltd. in the U.S. District Court for the District of Delaware asserting the infringement and validity of our patent covering a polymorphic form of tofacitinib, expiring in 2023, that was challenged by Sun Pharmaceutical Industries Ltd. in its abbreviated new drug application seeking approval to market a generic version of tofacitinib 11 mg extended release tablets. In November 2017, we brought an additional patent-infringement action against Sun Pharmaceuticals Industries Ltd. in the U.S. District Court for the District of Delaware asserting the infringement and validity of another patent challenged by Sun Pharmaceuticals Industries Ltd, which covers the active ingredient and expires in December 2025.

In March 2017, we brought a patent-infringement action against Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Ltd. (collectively, Zydus) in the U.S. District Court for the District of Delaware asserting the infringement and validity of the same

three patents that are the subject of the action against MicroLabs, which Zydus challenged in its abbreviated new drug application seeking approval to market a generic version of tofacitinib 5 mg tablets.

Also, in March 2017, we brought separate actions in the U.S. District Court for the District of Delaware against Prinston Pharmaceutical Inc., Zhejiang Huahai Pharmaceutical Co., Ltd., Huahai US Inc. and Solco Healthcare US, LLC (collectively, Prinston) and against Breckenridge Pharmaceutical Inc., Pensa Pharma S.A. and Laboratorios Del Dr. Esteve, S.A. (collectively, Breckenridge) on the two patents expiring in 2022 and 2023, respectively, that were challenged by Prinston and Breckenridge in their respective abbreviated new drug applications seeking approval to market generic versions of tofacitinib 5 mg tablets. In October 2017, we brought an additional patent-infringement action against Breckenridge in the U.S. District Court for the District of Delaware asserting the infringement and validity of four additional patents challenged by Breckenridge, three of which expire in December 2020 and one of which expires in December 2025. In March 2018, we brought another patent infringement action against Prinston in the U.S. District Court for the District of Delaware asserting the infringement and validity of an additional patent, which had been subsequently challenged by Prinston and which expires in December 2025. In May 2018, we settled all of our claims against Breckenridge on terms not material to Pfizer.

Xtandi (enzalutamide)
In December 2016, Medivation and Medivation Prostate Therapeutics, Inc. (collectively, the Medivation Group); Astellas Pharma Inc., Astellas US LLC and Astellas Pharma US, Inc. (collectively, Astellas); and The Regents of the University of California filed patent-infringement suits in the U.S. District Court for the District of Delaware against Actavis Laboratories FL, Inc. and Actavis LLC (collectively, Actavis); Zydus; and Apotex Inc. and Apotex Corp. (collectively, Apotex) in connection with those companies' respective abbreviated new drug applications filed with the FDA for approval to market generic versions of enzalutamide. The generic manufacturers are challenging patents, which expire as early as 2026, covering enzalutamide and treatments for prostate cancer. In May 2017, the Medivation Group filed a patent-infringement suit against Roxane Laboratories Inc. (Roxane) in the same court in connection with Roxane's abbreviated new drug application with the FDA for approval to market a generic version of enzalutamide. In June and July 2018, we settled all of our claims against Actavis and Apotex, respectively, on terms not material to Pfizer.

Inlyta (axitinib)
In April 2018, Apotex Inc. notified us that it had filed an abbreviated new drug application with the FDA seeking approval to market a generic version of Inlyta. Apotex Inc. asserts the invalidity and non-infringement of the crystalline form patent for Inlyta that expires in 2030. In May 2018, we filed suit against Apotex Inc. in the U.S. District Court for the District of Delaware, asserting the validity and infringement of the crystalline form patent for Inlyta.

Kerydin (tavaborole)
In September 2018, several generic companies notified us that they had filed abbreviated new drug applications with the FDA seeking approval to market generic versions of Kerydin. The generic companies assert the invalidity and non-infringement of methods of use and formulation patents for tavaborole that expire in 2026 and 2027, including pediatric exclusivity. In October 2018, Anacor, our wholly-owned subsidiary **,** filed infringement lawsuits against each of the generic filers in the U.S. District Court for the District of Delaware.

Matters Involving Our Collaboration/Licensing Partners

Toviaz (fesoterodine)—Inter-Partes Reviews
In January 2016, Mylan Pharmaceuticals and Mylan Laboratories (collectively, Mylan) filed petitions with the U.S. Patent and Trademark Office requesting inter partes reviews of five of the patents covering fesoterodine, the active ingredient in Toviaz: three composition-of-matter patents and a method-of-use patent that expire in 2019 and a patent covering salts of fesoterodine that expires in 2022. The patents are owned by UCB Pharma GmbH, and we have an exclusive, worldwide license to market Toviaz from UCB Pharma GmbH. In July 2016, the Patent Trial and Appeal Board agreed to institute inter partes reviews of all five patents. Amerigen Pharmaceuticals Limited (Amerigen), Alembic Pharmaceuticals Limited and Torrent Pharmaceuticals Limited joined the inter partes reviews. In July 2017, the U.S. Patent and Trademark Office issued decisions upholding all five patents. In September 2017, Mylan and Amerigen appealed the U.S. Patent and Trademark Office decisions to the U.S. Court of Appeals for the Federal Circuit . In January 2018, Mylan withdrew its appeal. Amerigen's appeal of the decision upholding the patent covering salts of fesoterodine that expires in 2022 is the only pending appeal.

Eliquis
In February, March, and April 2017, twenty-five generic companies sent BMS Paragraph-IV certification letters informing BMS that they had filed abbreviated new drug applications seeking approval of generic versions of Eliquis, challenging the validity and infringement of one or more of the three patents listed in the Orange Book for Eliquis. The patents currently are set to expire in 2019, 2026, and 2031. Eliquis has been jointly developed and is being commercialized by BMS and Pfizer. In April 2017, BMS and Pfizer filed patent-infringement actions against all generic filers in the U.S. District Court for the District of

Delaware and the U.S. District Court for the District of West Virginia, asserting that each of the generic companies' proposed products would infringe each of the patent(s) that each generic filer challenged. Some generic filers challenged only the 2031 patent, some challenged both the 2031 and 2026 patent, and one generic company challenged all three patents. We and BMS have settled with certain of the generic companies on terms not material to Pfizer, and we and BMS may settle with other generic companies in the future.

Actions In Which We Are The Defendant

Inflectra (infliximab-dyyb)
In March 2015, Janssen and New York University, together, brought a patent-infringement action in the U.S. District Court for the District of Massachusetts against Hospira, Celltrion Healthcare Co. Ltd. and Celltrion Inc. alleging that infliximab-dyyb, to be marketed by Hospira in the U.S. under the brand name Inflectra, would infringe six patents relating to infliximab, its manufacture and use. Claims with respect to four of the patents were dismissed by the plaintiffs, leaving two patents at issue: the infliximab antibody patent and a patent relating to cell culture media. In January 2018, the antibody patent was declared invalid by the Court of Appeals for the Federal Circuit. In July 2018, the U.S. District Court for the District of Massachusetts granted defendants' motion for summary judgment and ruled that the patent relating to cell culture media was not infringed.

Bavencio (avelumab)
In July 2017, BMS, E.R. Squibb & Sons LLC, Ono Pharmaceutical Co. Ltd., and Tasuku Honjo brought a patent-infringement action in the U.S. District Court for the District of Delaware against Pfizer, Merck KGaA, and EMD Serono, Inc., alleging that Bavencio (avelumab) infringes one patent relating to methods for treating tumors with anti-PD-L1 antibodies, which expires in 2023.

A2. Legal Proceedings—Product Litigation

Like other pharmaceutical companies, we are defendants in numerous cases, including but not limited to those discussed below, related to our pharmaceutical and other products. Plaintiffs in these cases seek damages and other relief on various grounds for alleged personal injury and economic loss.

Asbestos
Between 1967 and 1982, Warner-Lambert owned American Optical Corporation (American Optical), which manufactured and sold respiratory protective devices and asbestos safety clothing. In connection with the sale of American Optical in 1982, Warner-Lambert agreed to indemnify the purchaser for certain liabilities, including certain asbestos-related and other claims. As of September 30, 2018 , approximately 56,880 claims naming American Optical and numerous other defendants were pending in various federal and state courts seeking damages for alleged personal injury from exposure to asbestos and other allegedly hazardous materials. Warner-Lambert was acquired by Pfizer in 2000 and is a wholly-owned subsidiary of Pfizer. Warner-Lambert is actively engaged in the defense of, and will continue to explore various means of resolving, these claims.

Numerous lawsuits are pending against Pfizer in various federal and state courts seeking damages for alleged personal injury from exposure to products allegedly containing asbestos and other allegedly hazardous materials sold by Pfizer and certain of its previously owned subsidiaries.

There also are a small number of lawsuits pending in various federal and state courts seeking damages for alleged exposure to asbestos in facilities owned or formerly owned by Pfizer or its subsidiaries.

Effexor
Beginning in May 2011, actions, including purported class actions, were filed in various federal courts against Wyeth and, in certain of the actions, affiliates of Wyeth and certain other defendants relating to Effexor XR, which is the extended-release formulation of Effexor. The plaintiffs in each of the class actions seek to represent a class consisting of all persons in the U.S. and its territories who directly purchased, indirectly purchased or reimbursed patients for the purchase of Effexor XR or generic Effexor XR from any of the defendants from June 14, 2008 until the time the defendants' allegedly unlawful conduct ceased. The plaintiffs in all of the actions allege delay in the launch of generic Effexor XR in the U.S. and its territories, in violation of federal antitrust laws and, in certain of the actions, the antitrust, consumer protection and various other laws of certain states, as the result of Wyeth fraudulently obtaining and improperly listing certain patents for Effexor XR in the Orange Book, enforcing certain patents for Effexor XR and entering into a litigation settlement agreement with a generic drug manufacturer with respect to Effexor XR. Each of the plaintiffs seeks treble damages (for itself in the individual actions or on behalf of the putative class in the purported class actions) for alleged price overcharges for Effexor XR or generic Effexor XR in the U.S. and its territories since June 14, 2008. All of these actions have been consolidated in the U.S. District Court for the District of New Jersey.

In October 2014, the District Court dismissed the direct purchaser plaintiffs' claims based on the litigation settlement agreement but declined to dismiss the other direct purchaser plaintiff claims. In January 2015, the District Court entered partial final

judgments as to all settlement agreement claims, including those asserted by direct purchasers and end-payer plaintiffs, which plaintiffs appealed to the U.S. Court of Appeals for the Third Circuit. In August 2017, the U.S. Court of Appeals for the Third Circuit reversed the District Court's decisions and remanded the claims to the District Court.

Lipitor

- *Antitrust Actions*

Beginning in November 2011, purported class actions relating to Lipitor were filed in various federal courts against, among others, Pfizer, certain affiliates of Pfizer, and, in most of the actions, Ranbaxy, Inc. (Ranbaxy) and certain affiliates of Ranbaxy. The plaintiffs in these various actions seek to represent nationwide, multi-state or statewide classes consisting of persons or entities who directly purchased, indirectly purchased or reimbursed patients for the purchase of Lipitor (or, in certain of the actions, generic Lipitor) from any of the defendants from March 2010 until the cessation of the defendants' allegedly unlawful conduct (the Class Period). The plaintiffs allege delay in the launch of generic Lipitor, in violation of federal antitrust laws and/or state antitrust, consumer protection and various other laws, resulting from (i) the 2008 agreement pursuant to which Pfizer and Ranbaxy settled certain patent litigation involving Lipitor, and Pfizer granted Ranbaxy a license to sell a generic version of Lipitor in various markets beginning on varying dates, and (ii) in certain of the actions, the procurement and/or enforcement of certain patents for Lipitor. Each of the actions seeks, among other things, treble damages on behalf of the putative class for alleged price overcharges for Lipitor (or, in certain of the actions, generic Lipitor) during the Class Period. In addition, individual actions have been filed against Pfizer, Ranbaxy and certain of their affiliates, among others, that assert claims and seek relief for the plaintiffs that are substantially similar to the claims asserted and the relief sought in the purported class actions described above. These various actions have been consolidated for pre-trial proceedings in a Multi-District Litigation (*In re Lipitor Antitrust Litigation MDL-2332*) in the U.S. District Court for the District of New Jersey.

In September 2013 and 2014, the District Court dismissed with prejudice the claims by direct purchasers. In October and November 2014, the District Court dismissed with prejudice the claims of all other Multi-District Litigation plaintiffs. All plaintiffs have appealed the District Court's orders dismissing their claims with prejudice to the U.S. Court of Appeals for the Third Circuit. In addition, the direct purchaser class plaintiffs appealed the order denying their motion to amend the judgment and for leave to amend their complaint to the U.S. Court of Appeals for the Third Circuit. In August 2017, the U.S. Court of Appeals for the Third Circuit reversed the District Court's decisions and remanded the claims to the District Court.

Also, in January 2013, the State of West Virginia filed an action in West Virginia state court against Pfizer and Ranbaxy, among others, that asserts claims and seeks relief on behalf of the State of West Virginia and residents of that state that are substantially similar to the claims asserted and the relief sought in the purported class actions described above.

- *Personal Injury Actions*

A number of individual and multi-plaintiff lawsuits have been filed against us in various federal and state courts alleging that the plaintiffs developed type 2 diabetes purportedly as a result of the ingestion of Lipitor. Plaintiffs seek compensatory and punitive damages.

In February 2014, the federal actions were transferred for consolidated pre-trial proceedings to a Multi-District Litigation (*In re Lipitor (Atorvastatin Calcium) Marketing, Sales Practices and Products Liability Litigation (No. II) MDL-2502*) in the U.S. District Court for the District of South Carolina. Since 2016, certain cases in the Multi-District Litigation were remanded to certain state courts. In January 2017, the District Court granted our motion for summary judgment, dismissing substantially all of the remaining cases pending in the Multi-District Litigation. In January 2017, the plaintiffs appealed the District Court's decision to the U.S. Court of Appeals for the Fourth Circuit. In June 2018, the U.S. Court of Appeals for the Fourth Circuit affirmed the District Court's decision.

Viagra

A number of individual and multi-plaintiff lawsuits have been filed against us in various federal and state courts alleging that the plaintiffs developed melanoma and/or the exacerbation of melanoma purportedly as a result of the ingestion of Viagra. Plaintiffs seek compensatory and punitive damages.

In April 2016, the federal actions were transferred for coordinated pre-trial proceedings to a Multi-District Litigation (*In Re: Viagra (Sildenafil Citrate) Products Liability Litigation, MDL-2691*) in the U.S. District Court for the Northern District of California. In December 2016, federal actions filed against Lilly and filed against both us and Lilly, were transferred for coordinated pre-trial proceedings to the Multi-District Litigation (*In re: Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Products Liability Litigation, MDL-2691*).

Intravenous Solutions

Beginning in November 2016, purported class actions were filed in the U.S. District Court for the Northern District of Illinois against Hospira, Hospira Worldwide, Inc. and certain other defendants relating to intravenous saline solution. Plaintiffs seek to

represent a class consisting of all persons and entities in the U.S. who directly purchased intravenous saline solution sold by any of the defendants from January 1, 2013 until the time the defendants' allegedly unlawful conduct ceases. Plaintiffs allege that the defendants' conduct restricts output and artificially fixes, raises, maintains and/or stabilizes the prices of intravenous saline solution sold throughout the U.S. in violation of federal antitrust laws. Plaintiffs seek treble damages (for themselves and on behalf of the putative classes) and an injunction against defendants for alleged price overcharges for intravenous saline solution in the U.S. since January 1, 2013. All of these actions have been consolidated in the U.S. District Court for the Northern District of Illinois. In July 2018, the District Court granted defendants' motions to dismiss the consolidated amended complaint without prejudice. Plaintiffs filed a second amended complaint in September 2018. On February 3, 2017, we completed the sale of our global infusion systems net assets, HIS, which includes intravenous saline solution, to ICU Medical. The litigation is the subject of cross-claims for indemnification by both Pfizer and ICU Medical under the purchase agreement.

Separately, in April 2017, Pfizer, Hospira and two employees of Pfizer received grand jury subpoenas issued by the United States District Court for the Eastern District of Pennsylvania, in connection with an investigation by the U.S. Department of Justice, Antitrust Division. The subpoenas seek documents related to the sale, manufacture, pricing and shortages of intravenous solutions, including saline, as well as communications among industry participants regarding these issues. The Department of Justice investigation is also the subject of cross-claims for indemnification by both Pfizer and ICU Medical under the purchase agreement. In addition, in August 2015, the New York Attorney General issued a subpoena to Hospira for similar information. Hospira has produced records to the New York Attorney General and coordinated with ICU Medical to produce records to the U.S. Department of Justice.

Hormone Therapy Consumer Class Action
A certified consumer class action is pending against Wyeth in the U.S. District Court for the Southern District of California based on the alleged off-label marketing of its hormone therapy products. The case was originally filed in December 2003. The class consists of California consumers who purchased Wyeth's hormone-replacement products between January 1995 and January 2003 and who do not seek personal injury damages therefrom. The class seeks compensatory and punitive damages, including a full refund of the purchase price.

Eliquis
A number of individual and multi-plaintiff lawsuits have been filed against us and BMS in various federal and state courts pursuant to which plaintiffs seek to recover for personal injuries, including wrongful death, due to bleeding allegedly as a result of the ingestion of Eliquis. Plaintiffs seek compensatory and punitive damages.

In February 2017, the federal actions were transferred for coordinated pre-trial proceedings to a Multi-District Litigation (*In Re: Eliquis (Apixaban) Products Liability Litigation MDL-2754*) in the U.S. District Court for the Southern District of New York. In July 2017, the District Court dismissed substantially all of the actions that were pending in the Multi-District Litigation. In August 2017, certain plaintiffs appealed the District Court's dismissal to the U.S. Court of Appeals for the Second Circuit. Additional cases continue to be transferred to the Multi-District Litigation.

EpiPen
Beginning in February 2017, purported class actions were filed in various federal courts by indirect purchasers of EpiPen against Pfizer, and/or its affiliates King and Meridian, and/or various entities affiliated with Mylan N.V., and Mylan N.V. Chief Executive Officer, Heather Bresch. The plaintiffs in these actions seek to represent U.S. nationwide classes comprising persons or entities who paid for any portion of the end-user purchase price of an EpiPen between 2009 until the cessation of the defendants' allegedly unlawful conduct. In August 2017, a similar lawsuit brought in the U.S. District Court for the District of New Jersey on behalf of a purported class of direct purchaser plaintiffs against Pfizer, King, Meridian and Mylan was voluntarily dismissed without prejudice. Against Pfizer and/or its affiliates, plaintiffs generally allege that Pfizer's and/or its affiliates' settlement of patent litigation regarding EpiPen delayed market entry of generic EpiPen in violation of federal antitrust laws and various state antitrust or consumer protection laws. At least one lawsuit also alleges that Pfizer and/or Mylan N.V. violated the federal Racketeer Influenced and Corrupt Organizations Act. Plaintiffs also filed various consumer protection and unjust enrichment claims against, and relating to conduct attributable solely to, Mylan Pharmaceuticals regarding EpiPen. Plaintiffs seek treble damages for alleged overcharges for EpiPen since 2009. In August 2017, the actions were consolidated for coordinated pre-trial proceedings in a Multi-District Litigation (*In re: EpiPen (Epinephrine Injection, USP) Marketing, Sales Practices and Antitrust Litigation* , MDL-2785) in the U.S. District Court for the District of Kansas with other EpiPen-related actions against Mylan N.V. and/or its affiliates to which Pfizer, King and Meridian are not parties.

Nexium 24HR and Protonix
A number of individual and multi-plaintiff lawsuits have been filed against Pfizer, certain of its subsidiaries and/or other pharmaceutical manufacturers in various federal and state courts alleging that the plaintiffs developed kidney-related injuries purportedly as a result of the ingestion of certain proton pump inhibitors. The cases against us involve Nexium 24HR and/or Protonix and seek compensatory and punitive damages and, in some cases, treble damages, restitution or disgorgement. In

August 2017, the federal actions were ordered transferred for coordinated pre-trial proceedings to a Multi-District Litigation (*In re: Proton-Pump Inhibitor Products Liability Litigation* (No. II)) in the U.S. District Court for the District of New Jersey.

Docetaxel

- *Personal Injury Actions*

A number of lawsuits have been filed against Hospira and Pfizer in various federal and state courts alleging that plaintiffs who were treated with Docetaxel developed permanent hair loss. The significant majority of the cases also name other defendants, including the manufacturer of the branded product, Taxotere. Plaintiffs seek compensatory and punitive damages.

In October 2016, the federal cases were transferred for coordinated pre-trial proceedings to a Multi-District Litigation (*In re Taxotere (Docetaxel) Products Liability Litigation* , MDL-2740) in the U.S. District Court for the Eastern District of Louisiana.

- *Mississippi Attorney General Government Investigation*

In October 2018, the Attorney General of Mississippi filed a complaint in Mississippi state court against the manufacturer of the branded product and eight other manufacturers including Pfizer and Hospira, alleging, with respect to Pfizer and Hospira, a failure to warn about a risk of permanent hair loss in violation of the Mississippi Consumer Protection Act. The action seeks civil penalties and injunctive relief.

A3. Legal Proceedings—Commercial and Other Matters

Average Wholesale Price Litigation

Pfizer, certain of its subsidiaries and other pharmaceutical manufacturers were sued in various state courts by a number of states alleging that the defendants provided average wholesale price (AWP) information for certain of their products that was higher than the actual average prices at which those products were sold. The AWP is used to determine reimbursement levels under Medicare Part B and Medicaid and in many private-sector insurance policies and medical plans. All but one of those actions have been resolved through settlement, dismissal or final judgment. The plaintiff state, Illinois, in the one remaining action claims that the alleged spread between the AWPs at which purchasers were reimbursed and the actual sale prices was promoted by the defendants as an incentive to purchase certain of their products. The action alleges, among other things, fraud and violation of the state's unfair trade practices and consumer protection statutes and seeks monetary and other relief, including civil penalties and treble damages.

Monsanto-Related Matters

In 1997, Monsanto Company (Former Monsanto) contributed certain chemical manufacturing operations and facilities to a newly formed corporation, Solutia Inc. (Solutia), and spun off the shares of Solutia. In 2000, Former Monsanto merged with Pharmacia & Upjohn Company to form Pharmacia. Pharmacia then transferred its agricultural operations to a newly created subsidiary, named Monsanto Company (New Monsanto), which it spun off in a two-stage process that was completed in 2002. Pharmacia was acquired by Pfizer in 2003 and is a wholly-owned subsidiary of Pfizer.

In connection with its spin-off that was completed in 2002, New Monsanto assumed, and agreed to indemnify Pharmacia for, any liabilities related to Pharmacia's former agricultural business. New Monsanto has defended and/or is defending Pharmacia in connection with various claims and litigation arising out of, or related to, the agricultural business, and has been indemnifying Pharmacia when liability has been imposed or settlement has been reached regarding such claims and litigation.

In connection with its spin-off in 1997, Solutia assumed, and agreed to indemnify Pharmacia for, liabilities related to Former Monsanto's chemical businesses. As the result of its reorganization under Chapter 11 of the U.S. Bankruptcy Code, Solutia's indemnification obligations relating to Former Monsanto's chemical businesses are primarily limited to sites that Solutia has owned or operated. In addition, in connection with its spinoff that was completed in 2002, New Monsanto assumed, and agreed to indemnify Pharmacia for, any liabilities primarily related to Former Monsanto's chemical businesses, including, but not limited to, any such liabilities that Solutia assumed. Solutia's and New Monsanto's assumption of, and agreement to indemnify Pharmacia for, these liabilities apply to pending actions and any future actions related to Former Monsanto's chemical businesses in which Pharmacia is named as a defendant, including, without limitation, actions asserting environmental claims, including alleged exposure to polychlorinated biphenyls. Solutia and/or New Monsanto are defending Pharmacia in connection with various claims and litigation arising out of, or related to, Former Monsanto's chemical businesses, and have been indemnifying Pharmacia when liability has been imposed or settlement has been reached regarding such claims and litigation.

Environmental Matters

In 2009, we submitted to the U.S. Environmental Protection Agency (EPA) a corrective measures study report with regard to Pharmacia's discontinued industrial chemical facility in North Haven, Connecticut. In September 2010, our corrective measures study report was approved by the EPA, and we commenced construction of the site remedy in late 2011 under an Updated Administrative Order on Consent with the EPA.

Also, in 2009, we submitted a revised site-wide feasibility study with regard to Wyeth Holdings Corporation's (formerly, American Cynamid Company) discontinued industrial chemical facility in Bound Brook, New Jersey. In July 2011, Wyeth Holdings Corporation finalized an Administrative Settlement Agreement with the EPA and Order on Consent for Removal Action (the 2011 Administrative Settlement Agreement) with the EPA with regard to the Bound Brook facility. In May 2012, we completed construction of an interim remedy to address the discharge of impacted groundwater from that facility to the Raritan River. In September 2012, the EPA issued a final remediation plan for the Bound Brook facility's main plant area, which is generally in accordance with one of the remedies evaluated in our revised site-wide feasibility study. In March 2013, Wyeth Holdings Corporation (now Wyeth Holdings LLC) entered into an Administrative Settlement Agreement and Order on Consent with the EPA to allow us to undertake detailed engineering design of the remedy for the main plant area and to perform a focused feasibility study for two adjacent lagoons. In September 2015, the U.S., on behalf of the EPA, filed a complaint and consent decree with the federal District Court for the District of New Jersey that allows Wyeth Holdings LLC to complete the design and to implement the remedy for the main plant area. In December 2015, the consent decree (which supersedes the 2011 Administrative Settlement Agreement) was entered by the District Court. We have accrued for the estimated costs of the site remedies for the North Haven and Bound Brook facilities. In September 2018, the EPA issued a final remediation plan for the two adjacent lagoons, which is generally in accordance with one of the remedies evaluated in our focused feasibility study.

We are a party to a number of other proceedings brought under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended, and other state, local or foreign laws in which the primary relief sought is the cost of past and/or future remediation.

Contracts with Iraqi Ministry of Health
In October 2017, a number of United States service members, civilians, and their families brought a complaint in the Federal District Court for the District of Columbia against a number of pharmaceutical and medical devices companies, including Pfizer and certain of its subsidiaries, alleging that the defendants violated the United States Anti-Terrorism Act. The complaint alleges that the defendants provided funding for terrorist organizations through their sales practices pursuant to pharmaceutical and medical device contracts with the Iraqi Ministry of Health, and seeks monetary relief. In July 2018, the U.S. Department of Justice requested documents related to this matter, which are being provided.

Allergan Complaint for Indemnity
In August 2018, Pfizer was named as a defendant in a third-party complaint for indemnity, along with King Pharmaceuticals LLC, a Pfizer subsidiary (King), filed by Allergan Finance LLC (Allergan) in a Multi-District Litigation (*In re National Prescription Opiate Litigation MDL 2804*) in the U.S. District Court for the Northern District of Ohio. The lawsuit asserts claims for indemnity related to Kadian, which was owned for a short period by King in 2008, prior to Pfizer's acquisition of King in 2010.

A4. Legal Proceedings—Government Investigations

Like other pharmaceutical companies, we are subject to extensive regulation by government agencies in the U.S., other developed markets and multiple emerging markets in which we operate. As a result, we have interactions with government agencies on an ongoing basis. Criminal charges, and substantial fines and/or civil penalties, as well as limitations on our ability to conduct business in applicable jurisdictions, could result from government investigations. In addition, in a qui tam lawsuit in which the government declines to intervene, the relator may still pursue a suit for the recovery of civil damages and penalties on behalf of the government. Among the investigations by government agencies are the matters discussed below.

Phenytoin Sodium Capsules
In 2012, Pfizer sold the U.K. Marketing Authorisation for phenytoin sodium capsules to a third party, but retained the right to supply the finished product to that third party. In May 2013, the U.K. Competition & Markets Authority (CMA) informed us that it had launched an investigation into the supply of phenytoin sodium capsules in the U.K. market. In August 2015, the CMA issued a Statement of Objections alleging that Pfizer and Pfizer Limited, a U.K. subsidiary, engaged in conduct that violates U.K. and EU antitrust laws. In December 2016, the CMA imposed a £84.2 million fine on Pfizer and Pfizer Limited. Pfizer appealed the CMA decision to The Competition Appeal Tribunal in February 2017 . On June 7, 2018, the Competition Appeal Tribunal overturned the CMA decision as well as the associated fine. On June 28, 2018, the CMA sought permission to appeal the Competition Appeal Tribunal's judgment.

Greenstone Investigations
Since July 2017, the U.S. Department of Justice's Antitrust Division has been investigating our Greenstone generics business. We believe this is related to an ongoing antitrust investigation of the generic pharmaceutical industry. The government has been obtaining information from Greenstone. In April 2018, Greenstone received requests for information from the Antitrust Department of the Connecticut Office of the Attorney General. We have been providing information pursuant to these requests.

Subpoena relating to Manufacturing of Quillivant XR
In October 2018, we received a subpoena from the U.S. Attorney's Office for the Southern District of New York seeking records relating to our relationship with another drug manufacturer and its production and manufacturing of drugs including, but not limited to, Quillivant XR. We will be producing records pursuant to the subpoena.

Intravenous Solutions
See *Note 12A2. Legal Proceedings — Product Litigation — Intravenous Solutions* above for information regarding government investigations related to sales of intravenous solution products.

Contracts with Iraqi Ministry of Health
See *Note 12A3. Legal Proceedings—Commercial and Other Matters—Contracts with Iraqi Ministry of Health* above for information regarding U.S. government investigations related to contracts with the Iraqi Ministry of Health.

Docetaxel — Mississippi Attorney General Government Investigation
See *Note 12A2. Legal Proceedings — Product Litigation — Docetaxel — Mississippi Attorney General Government Investigation* above for information regarding a government investigation related to Docetaxel marketing practices.

A5. Legal Proceedings--Matters Resolved During the First Nine Months of 2018

During 2018, certain matters, including the matters discussed below, were resolved or were the subject of definitive settlement agreements or settlement agreements-in-principle.

Celebrex
Beginning in July 2014, purported class actions were filed in the U.S. District Court for the Eastern District of Virginia against Pfizer and certain subsidiaries of Pfizer relating to Celebrex. The plaintiffs sought to represent U.S. nationwide or multi-state classes consisting of persons or entities who directly purchased from the defendants, or indirectly purchased or reimbursed patients for some or all of the purchase price of, Celebrex or generic Celebrex from May 31, 2014 until the cessation of the defendants' allegedly unlawful conduct. The plaintiffs alleged delay in the launch of generic Celebrex in violation of federal antitrust laws or certain state antitrust, consumer protection and various other laws as a result of Pfizer fraudulently obtaining and improperly listing a patent on Celebrex, engaging in sham litigation and prolonging the impact of sham litigation through settlement activity that further delayed generic entry. Each of the actions sought treble damages on behalf of the putative class for alleged price overcharges for Celebrex since May 31, 2014. In December 2014, the District Court granted the parties' joint motions to consolidate the direct purchaser and end-payer cases, and all such cases were consolidated as of March 2015. In October 2014 and March 2015, we filed motions to dismiss the direct purchasers' and end-payers' amended complaints, respectively. In November 2015, the District Court denied in part and granted in part our motion to dismiss the direct purchasers' amended complaint. In February 2016, the District Court denied in part and granted in part our motion to dismiss the end-payers' amended complaint, and in August 2016, the District Court dismissed substantially all of the end-payers' remaining claims. In February 2017, the District Court dismissed with prejudice all of the end-payers' claims. In March 2017, the end-payers appealed the District Court's order dismissing their claims with prejudice to the U.S. Court of Appeals for the Fourth Circuit. In August 2017, the District Court granted the direct purchasers' motion for class certification. In November 2017, Pfizer and the direct purchasers entered into an agreement to resolve the direct purchasers' class action for $94 million . In April 2018, the court approved the agreement. In November 2017, Pfizer and the end-payers entered into an agreement to resolve the claims of the end-payer plaintiffs on terms not material to Pfizer.

Subpoenas relating to Copayment Assistance Organizations
In December 2015 and July 2016, Pfizer received subpoenas from the U.S. Attorney's Office for the District of Massachusetts requesting documents related to the Patient Access Network Foundation and other 501(c)(3) organizations that provide financial assistance to Medicare patients. In May 2018, Pfizer entered into a civil settlement to resolve the matter. Pfizer paid $23.85 million to the United States, and entered into a five -year Corporate Integrity Agreement with the Office of the Inspector General of the Department of Health and Human Services.

Civil Investigative Demand relating to Pharmacy Benefit Managers
In March 2016, Pfizer received a Civil Investigative Demand from the U.S. Attorney's Office for the Southern District of New York (SDNY) related to Pfizer's contractual relationships with pharmacy benefit managers with respect to certain pharmaceutical products over the period from January 1, 2006 to the present. We have provided information to the government in response to this Civil Investigative Demand. In July 2018, Pfizer was served with a qui tam complaint that appears to be related to the SDNY investigation. The complaint was unsealed following the government's decision not to intervene in the case.

B. Guarantees and Indemnifications

In the ordinary course of business and in connection with the sale of assets and businesses and other transactions, we often indemnify our counterparties against certain liabilities that may arise in connection with the transaction or that are related to events and activities prior to or following a transaction. If the indemnified party were to make a successful claim pursuant to the terms of the indemnification, we may be required to reimburse the loss. These indemnifications are generally subject to various restrictions and limitations. Historically, we have not paid significant amounts under these provisions and, as of September 30, 2018 , the estimated fair value of these indemnification obligations was not significant.

Pfizer Inc. has also guaranteed the long-term debt of certain companies that it acquired and that now are subsidiaries of Pfizer.

C. Certain Commitments

- Accelerated share repurchase agreement —On March 12, 2018 , we entered into an accelerated share repurchase agreement with Citibank to repurchase $4.0 billion of our common stock. Pursuant to the terms of the agreement, on March 14, 2018 , we paid $4.0 billion to Citibank and received an initial delivery of approximately 87 million shares of our common stock from Citibank at a price of $36.61 per share, which represented, based on the closing price of our common stock on the NYSE on March 12, 2018 , approximately 80% of the notional amount of the accelerated share repurchase agreement. On September 5, 2018, the accelerated share repurchase agreement with Citibank was completed, which, per the terms of the agreement, resulted in Citibank owing us a certain number of shares of Pfizer common stock. Pursuant to the agreement's settlement terms, we received an additional 21 million shares of our common stock from Citibank on September 7, 2018. The average price paid for all of the shares delivered under the accelerated share repurchase agreement was $36.86 per share. The common stock received is included in *Treasury stock* . This agreement was entered into pursuant to our previously announced share repurchase authorization. After giving effect to the accelerated share repurchase agreement, as well as other share repurchases through September 30, 2018 , our remaining share-purchase authorization was approximately $9.2 billion at September 30, 2018 .
- Corporate headquarters lease agreement —In April 2018, we entered an agreement to lease space in an office building in the Hudson Yards neighborhood of New York City. We will relocate our global headquarters to this property with occupancy expected beginning in 2022. Our future minimum rental commitment under this 20 -year lease is approximately $1.7 billion . In July 2018, we completed the sale of our current headquarters at 219 and 235 East 42nd Street. We also agreed to lease these properties from the buyer while we complete our relocation.

Note 13. Segment, Geographic and Other Revenue Information

A. Segment Information

We manage our commercial operations through two distinct business segments: Pfizer Innovative Health (IH) and Pfizer Essential Health (EH). The IH and EH segments are each led by a single manager. Each operating segment has responsibility for its commercial activities and for certain IPR&D projects for new investigational products and additional indications for in-line products that generally have achieved proof-of-concept. Each business has a geographic footprint across developed and emerging markets. Our chief operating decision maker uses the revenues and earnings of the two operating segments, among other factors, for performance evaluation and resource allocation.

We regularly review our segments and the approach used by management for performance evaluation and resource allocation. In July 2018, we announced that we will reorganize our commercial operations effective at the beginning of our 2019 fiscal year. We will organize the company into three businesses: a science-based Innovative Medicines business, which will include all of the current Pfizer Innovative Health medicines and vaccines business units as well as biosimilars and a new hospital business unit for anti-infectives and sterile injectables; an off-patent branded and generic Established Medicines business operating with substantial autonomy within Pfizer; and a Consumer Healthcare business. We are currently evaluating the impact to our operating segments and other costs and activities based on how the businesses will be managed in 2019.

As described in *Note 1A* , the February 3, 2017 sale of HIS impacted our results of operations in 2017.

Operating Segments

Some additional information about our business segments as of September 30, 2018 follows:

Pfizer Innovative Health	Pfizer ESSENTIAL HEALTH
IH focuses on developing and commercializing novel, value-creating medicines and vaccines that significantly improve patients' lives, as well as products for consumer healthcare. Key therapeutic areas include internal medicine, vaccines, oncology, inflammation & immunology, rare disease and consumer healthcare.	EH includes legacy brands that have lost or will soon lose market exclusivity in both developed and emerging markets, branded and generic sterile injectable products, biosimilars, and select branded products including anti-infectives. EH also includes an R&D organization, as well as our contract manufacturing business. Through February 2, 2017, EH also included HIS.
Leading brands include: - *Prevnar 13/Prevenar 13* - *Xeljanz* - *Eliquis* - *Lyrica* (U.S., Japan and certain other markets) - *Enbrel* (outside the U.S. and Canada) - *Ibrance* - *Xtandi* - Several OTC consumer healthcare products (e.g., *Advil* and *Centrum*)	**Leading brands include:** - *Lipitor* - *Norvasc* - *Lyrica* (Europe, Russia, Turkey, Israel and Central Asia countries) - *Celebrex* - *Viagra** - *Inflectra/Remsima* - *Sulperazon* - Several other sterile injectable products

* Viagra lost exclusivity in the U.S. in December 2017. Beginning in 2018, revenues for Viagra in the U.S. and Canada, which were reported in IH through 2017, are reported in EH (which reported all other Viagra revenues excluding the U.S. and Canada through 2017). Therefore, beginning in 2018, total Viagra worldwide revenues are reported in EH.

The following organizational change impacted our operating segments in 2018:

- Effective in the first quarter of 2018, certain costs for Pfizer's StratCO group, which were previously reported in the operating results of our operating segments and Corporate, are reported in Other Unallocated. StratCO costs primarily include headcount costs, vendor costs and data costs largely in support of Pfizer's commercial operations. The majority of the StratCO costs reflect additional amounts that our operating segments would have incurred had each segment operated as a standalone company during the periods presented. The reporting change was made to streamline accountability and speed decision making. In the third quarter of 2017, we reclassified approximately $125 million of costs from IH, approximately $36 million of costs from EH and approximately $19 million of costs from Corporate to Other unallocated costs to conform to the current period presentation. In the first nine months of 2017, we reclassified approximately $344 million of costs from IH, approximately $114 million of costs from EH and approximately $40 million of costs from Corporate to Other unallocated costs to conform to the current period presentation.

Other Costs and Business Activities

Certain pre-tax costs are not allocated to our operating segment results, such as costs associated with the following:

- WRD, which is generally responsible for research projects for our IH business until proof-of-concept is achieved and then for transitioning those projects to the IH segment via the GPD organization for possible clinical and commercial development. R&D spending may include upfront and milestone payments for intellectual property rights. The WRD organization also has responsibility for certain science-based and other platform-services organizations, which provide technical expertise and other services to the various R&D projects, including EH R&D projects. WRD is also responsible for facilitating all regulatory submissions and interactions with regulatory agencies, including all safety-event activities.
- GPD, which is generally responsible for the clinical development of assets that are in clinical trials for our WRD and Innovative portfolios. GPD also provides technical support and other services to Pfizer R&D projects.
- Corporate, representing platform functions (such as worldwide technology, global real estate operations, legal, finance, human resources, worldwide public affairs, compliance and worldwide procurement), the provision of medical information to healthcare providers, patients and other parties, transparency and disclosure activities, clinical trial results publication, grants for healthcare quality improvement and medical education, and partnerships with global public health and medical associations, as well as certain compensation and other corporate costs, such as interest income and expense, and gains and losses on investments. Effective in the first quarter of 2018, certain costs for StratCO, which were previously reported in the operating results of our operating segments and Corporate, are reported in Other Unallocated. For additional information, see note below on Other unallocated costs.

- Other unallocated costs, representing overhead expenses associated with our manufacturing and commercial operations that are not directly assessed to an operating segment, as business unit (segment) management does not manage these costs (which include manufacturing variances associated with production). In connection with the StratCO reporting change, in the third quarter of 2017, we reclassified approximately $125 million of costs from IH, approximately $36 million of costs from EH and approximately $19 million of costs from Corporate to Other unallocated costs to conform to the current period presentation. In the first nine months of 2017, we reclassified approximately $344 million of costs from IH, approximately $114 million of costs from EH and approximately $40 million of costs from Corporate to Other unallocated costs to conform to the current period presentation.
- Certain transactions and events such as (i) purchase accounting adjustments, where we incur expenses associated with the amortization of fair value adjustments to inventory, intangible assets and PP&E; (ii) acquisition-related costs, where we incur costs for executing the transaction, integrating the acquired operations and restructuring the combined company; and (iii) certain significant items, representing substantive and/or unusual, and in some cases recurring, items (such as restructuring or legal charges) that are evaluated on an individual basis by management and that, either as a result of their nature or size, would not be expected to occur as part of our normal business on a regular basis. Such items can include, but are not limited to, non-acquisition-related restructuring costs, as well as costs incurred for legal settlements, asset impairments and disposals of assets or businesses, including, as applicable, any associated transition activities.

Segment Assets

We manage our assets on a total company basis, not by operating segment, as many of our operating assets are shared (such as our plant network assets) or commingled (such as accounts receivable, as many of our customers are served by both operating segments). Therefore, our chief operating decision maker does not regularly review any asset information by operating segment and, accordingly, we do not report asset information by operating segment. Total assets were approximately $168 billion as of September 30, 2018 and $172 billion as of December 31, 2017 .

Selected Income Statement Information

The following table provides selected income statement information by reportable segment:

	Three Months Ended			
	Revenues		Earnings [a]	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Reportable Segments:				
IH [b]	$ 8,471	$ 8,118	$ 5,388	$ 5,000
EH [b]	4,826	5,050	2,527	2,801
Total reportable segments	13,298	13,168	7,915	7,801
Other business activities [c], [d]	—	—	(736)	(759)
Reconciling Items:				
Corporate [b], [d]	—	—	(1,337)	(1,363)
Purchase accounting adjustments [d]	—	—	(1,309)	(1,154)
Acquisition-related costs [d]	—	—	(112)	(155)
Certain significant items [e]	—	—	213	(449)
Other unallocated [b], [d]	—	—	(457)	(335)
	$ 13,298	$ 13,168	$ 4,177	$ 3,585

	Nine Months Ended			
	Revenues		Earnings [a]	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Reportable Segments:				
IH [b]	$ 24,573	$ 23,204	$ 15,419	$ 14,534
EH [b]	15,097	15,639	8,133	8,672
Total reportable segments	39,670	38,843	23,552	23,206
Other business activities [c], [d]	—	—	(2,130)	(2,205)
Reconciling Items:				
Corporate [b], [d]	—	—	(3,633)	(3,908)
Purchase accounting adjustments [d]	—	—	(3,665)	(3,527)
Acquisition-related costs [d]	—	—	(221)	(347)
Certain significant items [e]	—	—	(8)	(797)
Other unallocated [b], [d]	—	—	(1,064)	(1,070)
	$ 39,670	$ 38,843	$ 12,831	$ 11,351

[a] Income from continuing operations before provision for taxes on income. IH's earnings include d ividend income of $91 million and $54 million in the third quarter of 2018 and 2017 , respectively, and $226 million and $211 million in the first nine months of 2018 and 2017 , respectively, from our investment in ViiV. For additional information, see *Note 4.*

[b] In connection with the StratCO reporting change, in the third quarter of 2017, we reclassified approximately $125 million of costs from IH, approximately $36 million of costs from EH and approximately $19 million of costs from Corporate to Other unallocated costs to conform to the current period presentation. In the first nine months of 2017, we reclassified approximately $344 million of costs from IH, approximately $114 million of costs from EH and approximately $40 million of costs from Corporate to Other unallocated costs to conform to the current period presentation.

[c] Other business activities includes the costs managed by our WRD and GPD organizations.

[d] For a description, see the "Other Costs and Business Activities" section above.

[e] Certain significant items are substantive and/or unusual, and in some cases recurring, items (such as restructuring or legal charges) that, either as a result of their nature or size, would not be expected to occur as part of our normal business on a regular basis.

For Earnings in the third quarter of 2018 , certain significant items includes: (i) restructuring credits and implementation costs associated with our cost-reduction ini tiatives that are not associated with an acquisition of $35 million , (ii) net charges for certain legal matters of $37 million , (iii) income of $2 million , representing an adjustment t o amounts previously recorded to write down the HIS net assets to fair value less costs to sell and (iv) other income of $282 million , which includes, among other things, a non-cash $343 million pre-tax gain in *Other (income)/deductions—net* associated with our transaction with Bain Capital to create a new biopharmaceutical company, Cerevel, to continue development of a portfolio of clinical and preclinical stage neuroscience assets primarily targeting disorders of the central nervous system. For additional information, see *Note 2B, Note 3* and *Note 4.*

For Earnings in the third quarter of 2017 , certain significant items includes: (i) restructuring credits and implementation costs associated with our cost-reduction initiatives that are not associated with an acquisition of $55 million , (ii) charges for certain legal matters of $183 million , (iii) income of $12 million , representing an adjustment to amounts previously recorded to write down the HIS net assets to fair value less costs to sell, (iv) certain asset impairment charges of $127 million , (v) charges for business and legal entity alignment of $16 million and (vi) other charges of $81 million , which includes, among other things, $55 million in inventory losses, overhead costs related to the period in which our Puerto Rico plants were not operational, and incremental costs, all of which resulted from hurricanes in Puerto Rico and are included in *Cost of sales* . For additional information, see *Note 2B* , *Note 3* and *Note 4* .

For Earnings in the first nine months of 2018 , certain significant items includes: (i) restructuring credits and implementation costs associated with our cost-reduction initiatives that are not associated with an acquisition of $127 million , (ii) net credits for certain legal matters of $70 million , (iii) income of $1 million , representing an adjustment to amounts previously recorded to write down the HIS net assets to fair value less costs to sell, (iv) certain asset impairment charges of $31 million , (v) charges for business and legal entity alignment of $4 million and (vi) other income of $84 million , which includes, among other things, a non-cash $343 million pre-tax gain in *Other (income)/deductions—net* associated with our transaction with Bain Capital to create a new biopharmaceutical company, Cerevel, to continue development of a portfolio of clinical and preclinical stage neuroscience assets primarily targeting disorders of the central nervous system, a $119 million charge, in the aggregate, in *Selling, information and administrative expenses* , for a special one-time bonus paid to virtually all Pfizer colleagues, excluding executives, which was one of several actions taken by us after evaluating the expected positive net impact of the December 2017 enactment of the TCJA on us, and a $50 million pre-tax gain in *Other (income)/deductions—net* as a result of the contribution of our allogeneic chimeric antigen receptor T cell therapy development program assets in connection with our contribution agreement entered into with Allogene. For additional information, see *Note 2B* , *Note 3* and *Note 4* .

For Earnings in the first nine months of 2017 , certain significant items includes: (i) restructuring credits and implementation costs associated with our cost-reduction initiatives that are not associated with an acquisition of $133 million , (ii) charges for certain legal matters of $191 million , (iii) charges of $52 million , representing adjustments to amounts previously recorded to write-down the HIS net assets to fair value less costs to sell, (iv) certain asset impairment charges of $127 million , (v) charges for business and legal entity alignment of $54 million and (v) other charges of $239 million , which include, among other things, $55 million in inventory losses, overhead costs related to the period in which our Puerto Rico plants were not operational, and incremental costs, all of which resulted from hurricanes in Puerto Rico and are included in *Cost of sales* , and a net loss of $30 million related to the sale of our 40% ownership investment in Teuto, including the extinguishment of a put option for the then remaining 60% ownership interest, which is included in *Other (income)/deductions—net* . For additional information, see *Note 2B* , *Note 3* and *Note 4* .

Equity in the net income of investees accounted for by the equity method is not significant for any of our operating segments.

The operating segment information does not purport to represent the revenues, costs and income from continuing operations before provision for taxes on income that each of our operating segments would have recorded had each segment operated as a standalone company during the periods presented.

B. Geographic Information

As described in *Note 1A* , the February 3, 2017 sale of HIS impacted our results of operations in 2017.

The following table provides revenues by geographic area:

	Three Months Ended			Nine Months Ended		
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
U.S.	$ 6,361	$ 6,534	(3)	$ 18,861	$ 19,516	(3)
Developed Europe [a]	2,231	2,163	3	6,657	6,309	6
Developed Rest of World [b]	1,640	1,632	1	4,795	4,797	—
Emerging Markets [c]	3,066	2,839	8	9,358	8,222	14
Revenues	$ 13,298	$ 13,168	1	$ 39,670	$ 38,843	2

[a] Developed Europe region includes the following markets: Western Europe, Scandinavian countries and Finland. Revenues denominated in euros were $1.8 billion and $1.7 billion in the third quarter of 2018 and 2017 , respectively, and $5.3 billion and $5.0 billion in the first nine months of 2018 and 2017 , respectively.

[b] Developed Rest of World region includes the following markets: Japan, Canada, Australia, South Korea and New Zealand.

[c] Emerging Markets region includes, but is not limited to, the following markets: Asia (excluding Japan and South Korea), Latin America, Eastern Europe, Africa, the Middle East, Central Europe and Turkey.

C. Other Revenue Information

Significant Product Revenues

As described in *Note 1A* , the February 3, 2017 sale of HIS impacted our results of operations in 2017.

The following table provides detailed revenue information:

(MILLIONS OF DOLLARS)		Three Months Ended		Nine Months Ended	
PRODUCT	**PRIMARY INDICATIONS OR CLASS**	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
TOTAL REVENUES		**$ 13,298**	**$ 13,168**	**$ 39,670**	**$ 38,843**
PFIZER INNOVATIVE HEALTH (IH) [a]		**$ 8,471**	**$ 8,118**	**$ 24,573**	**$ 23,204**
Internal Medicine		**$ 2,463**	**$ 2,455**	**$ 7,339**	**$ 7,245**
Lyrica IH [b]	Epilepsy, post-herpetic neuralgia and diabetic peripheral neuropathy, fibromyalgia, neuropathic pain due to spinal cord injury	1,132	1,150	3,398	3,382
Eliquis alliance revenues and direct sales	Atrial fibrillation, deep vein thrombosis, pulmonary embolism	870	644	2,524	1,813
Chantix/Champix	An aid to smoking cessation treatment in adults 18 years of age or older	261	240	789	727
BMP2	Development of bone and cartilage	54	79	206	198
Toviaz	Overactive bladder	67	62	197	187
Viagra IH [c]	Erectile dysfunction	—	206	—	711
All other Internal Medicine	Various	79	75	224	228
Vaccines		**$ 1,845**	**$ 1,649**	**$ 4,708**	**$ 4,385**
Prevnar 13/Prevenar 13	Vaccines for prevention of pneumococcal disease	1,660	1,522	4,290	4,069
FSME/IMMUN-TicoVac	Tick-borne encephalitis vaccine	57	43	162	119
Trumenba	Meningococcal Group B vaccine	61	42	95	79
All other Vaccines	Various	67	43	160	117
Oncology		**$ 1,775**	**$ 1,616**	**$ 5,294**	**$ 4,551**
Ibrance	Advanced breast cancer	1,025	878	2,985	2,410
Sutent	Advanced and/or metastatic RCC, adjuvant RCC, refractory GIST (after disease progression on, or intolerance to, imatinib mesylate) and advanced pancreatic neuroendocrine tumor	248	276	785	805
Xtandi alliance revenues	Castration-resistant prostate cancer	180	150	510	422
Xalkori	ALK-positive and ROS1-positive advanced NSCLC	127	146	417	442
Inlyta	Advanced RCC	71	84	226	256
Bosulif	Philadelphia chromosome–positive chronic myelogenous leukemia	69	57	206	163
All other Oncology	Various	55	26	164	54
Inflammation & Immunology (I&I)		**$ 1,018**	**$ 1,000**	**$ 2,951**	**$ 2,863**
Enbrel (Outside the U.S. and Canada)	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, pediatric plaque psoriasis, ankylosing spondylitis and nonradiographic axial spondyloarthritis	531	613	1,589	1,818
Xeljanz	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis	432	348	1,221	935
Eucrisa	Mild-to-moderate atopic dermatitis (eczema)	40	15	104	33
All other I&I	Various	15	23	37	78
Rare Disease		**$ 531**	**$ 569**	**$ 1,651**	**$ 1,637**
BeneFIX	Hemophilia	132	151	420	453
Genotropin	Replacement of human growth hormone	143	136	416	375
Refacto AF/Xyntha	Hemophilia	117	140	388	409
Somavert	Acromegaly	64	65	195	182
All other Rare Disease	Various	74	77	232	218
Consumer Healthcare		**$ 839**	**$ 829**	**$ 2,631**	**$ 2,522**
PFIZER ESSENTIAL HEALTH (EH) [d]		**$ 4,826**	**$ 5,050**	**$ 15,097**	**$ 15,639**
Legacy Established Products (LEP) [e]		**$ 2,533**	**$ 2,681**	**$ 7,865**	**$ 7,995**
Lipitor	Reduction of LDL cholesterol	507	491	1,539	1,341
Norvasc	Hypertension	247	226	773	684
Premarin family	Symptoms of menopause	204	238	605	711
Xalatan/Xalacom	Glaucoma and ocular hypertension	76	83	233	241
Effexor	Depression and certain anxiety disorders	78	76	228	215

Zoloft	Depression and certain anxiety disorders	72	78	223	215
Zithromax	Bacterial infections	54	61	216	202
EpiPen	Epinephrine injection used in treatment of life-threatening allergic reactions	68	82	215	253
Xanax	Anxiety disorders	52	58	163	164
Sildenafil Citrate	Erectile dysfunction	1	—	72	—
All other LEP	Various	1,176	1,288	3,599	3,969

(MILLIONS OF DOLLARS)		Three Months Ended		Nine Months Ended	
PRODUCT	**PRIMARY INDICATIONS OR CLASS**	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Sterile Injectable Pharmaceuticals (SIP) [f]		**$ 1,239**	**$ 1,273**	**$ 3,928**	**$ 4,270**
Sulperazon	Treatment of infections	145	114	464	345
Medrol	Steroid anti-inflammatory	95	109	318	352
Fragmin	Slows blood clotting	76	79	221	221
Tygacil	Tetracycline class antibiotic	60	60	186	192
Zosyn/Tazocin	Antibiotic	55	47	175	124
Precedex	Sedation agent in surgery or intensive care	47	51	166	182
All other SIP	Various	761	814	2,399	2,852
Peri-LOE Products [g]		**$ 698**	**$ 794**	**$ 2,208**	**$ 2,398**
Viagra EH [c]	Erectile dysfunction	137	102	509	285
Celebrex	Arthritis pain and inflammation, acute pain	188	212	494	564
Vfend	Fungal infections	87	97	294	305
Lyrica EH [b]	Epilepsy, neuropathic pain and generalized anxiety disorder	81	134	251	428
Zyvox	Bacterial infections	50	68	184	220
Revatio	Pulmonary arterial hypertension	53	58	163	189
Pristiq	Depression	52	69	156	230
All other Peri-LOE Products	Various	49	55	157	176
Biosimilars [h]	Various	**$ 197**	**$ 141**	**$ 558**	**$ 367**
Inflectra/Remsima	Inflammatory diseases	166	112	469	284
All other Biosimilars	Various	31	28	89	82
Pfizer CentreOne [i]		**$ 159**	**$ 161**	**$ 539**	**$ 514**
Hospira Infusion Systems (HIS) [j]	Various	**$ —**	**$ —**	**$ —**	**$ 97**
Total Lyrica [b]	Epilepsy, post-herpetic neuralgia and diabetic peripheral neuropathy, fibromyalgia, neuropathic pain due to spinal cord injury	**$ 1,213**	**$ 1,285**	**$ 3,649**	**$ 3,810**
Total Viagra [c]	Erectile dysfunction	**$ 137**	**$ 308**	**$ 509**	**$ 996**
Total Alliance revenues	Various	**$ 977**	**$ 741**	**$ 2,820**	**$ 2,112**

[a] The IH business encompasses Internal Medicine, Vaccines, Oncology, Inflammation & Immunology, Rare Disease and Consumer Healthcare.
[b] Lyrica revenues from all of Europe, Russia, Turkey, Israel and Central Asia countries are included in Lyrica EH. All other Lyrica revenues are included in Lyrica IH. Total Lyrica revenues represent the aggregate of worldwide revenues from Lyrica IH and Lyrica EH.
[c] Viagra lost exclusivity in the U.S. in December 2017. Beginning in 2018, revenues for Viagra in the U.S. and Canada, which were reported in IH through 2017, are reported in EH (which reported all other Viagra revenues excluding the U.S. and Canada through 2017). Therefore, beginning in 2018, total Viagra revenues are reported in EH. Total Viagra revenues in 2017 represent the aggregate of worldwide revenues from Viagra IH and Viagra EH.
[d] The EH business encompasses Legacy Established Products, Sterile Injectable Pharmaceuticals, Peri-LOE Products, Biosimilars, Pfizer CentreOne and HIS (through February 2, 2017).
[e] Legacy Established Products primarily include products that have lost patent protection (excluding Sterile Injectable Pharmaceuticals and Peri-LOE Products). In the fourth quarter of 2017, we sold our equity share in Hisun Pfizer. As a result, effective in the first quarter of 2018, Hisun Pfizer-related revenues, previously reported in emerging markets within All Other LEP and All Other SIP, are reported in emerging markets within Pfizer CentreOne.
[f] Sterile Injectable Pharmaceuticals includes branded and generic injectables (excluding Peri-LOE Products). In the fourth quarter of 2017, we sold our equity share in Hisun Pfizer. As a result, effective in the first quarter of 2018, Hisun Pfizer-related revenues, previously reported in emerging markets within All Other LEP and All Other SIP, are reported in emerging markets within Pfizer CentreOne.
[g] Peri-LOE Products includes products that have recently lost or are anticipated to soon lose patent protection. These products primarily include: Lyrica in Europe, Russia, Turkey, Israel and Central Asia; worldwide revenues for Celebrex, Pristiq, Zyvox, Vfend, Revatio and Inspra; and beginning in 2018, Viagra revenues for all countries (and Viagra revenues for all countries other than the U.S. and Canada in 2017, see note (c) above).
[h] Biosimilars includes Inflectra/Remsima (biosimilar infliximab) in the U.S. and certain international markets, Nivestim (biosimilar filgrastim) in certain European, Asian and Africa/Middle Eastern markets and in the U.S. and Retacrit (biosimilar epoetin zeta) in certain European and Africa/Middle Eastern markets.
[i] Pfizer CentreOne includes revenues from our contract manufacturing and active pharmaceutical ingredient sales operation, including sterile injectables contract manufacturing, and revenues related to our manufacturing and supply agreements, including with Zoetis Inc. In the fourth quarter of 2017, we sold our equity share in Hisun Pfizer. As a result, effective in the first quarter of 2018, Hisun Pfizer-related revenues, previously reported in emerging markets within All Other LEP and All Other SIP, are reported in emerging markets within Pfizer CentreOne.
[j] HIS (through February 2, 2017) includes Medication Management Systems products composed of infusion pumps and related software and services, as well as IV Infusion Products, including large volume IV solutions and their associated administration sets.

REVIEW REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Shareholders of Pfizer Inc.:

Results of Review of Interim Financial Information

We have reviewed the condensed consolidated balance sheet of Pfizer Inc. and Subsidiary companies (the Company) as of September 30, 2018 , the related condensed consolidated statements of income and comprehensive income for the three-month and nine-month periods ended September 30, 2018 and October 1, 2017 , the related condensed consolidated statements of cash flows for the nine -month periods ended September 30, 2018 and October 1, 2017 and the related notes (collectively, the consolidated interim financial information). Based on our reviews, we are not aware of any material modifications that should be made to the consolidated interim financial information for it to be in conformity with U.S. generally accepted accounting principles.

We have previously audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheet of the Company as of December 31, 2017 , and the related consolidated statements of income, comprehensive income, equity, and cash flows for the year then ended (not presented herein); and in our report dated February 22, 2018, we expressed an unqualified opinion on those consolidated financial statements. In our opinion, the information set forth in the accompanying condensed consolidated balance sheet as of December 31, 2017 is fairly stated, in all material respects, in relation to the consolidated balance sheet from which it has been derived.

Basis for Review Results

This consolidated interim financial information is the responsibility of the Company’s management. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our reviews in accordance with the standards of the PCAOB. A review of consolidated interim financial information consists principally of applying analytical procedures and making inquiries of persons responsible for financial and accounting matters. It is substantially less in scope than an audit conducted in accordance with the standards of the PCAOB, the objective of which is the expression of an opinion regarding the financial statements taken as a whole. Accordingly, we do not express such an opinion.

/s/ KPMG LLP
New York, New York
November 8, 2018

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations

Introduction

See the Glossary of Defined Terms at the beginning of this Quarterly Report on Form 10-Q for terms used throughout this MD&A. Our MD&A is provided in addition to the accompanying condensed consolidated financial statements and footnotes to assist readers in understanding Pfizer's results of operations, financial condition and cash flows. The MD&A is organized as follows:

- *Overview of Our Performance, Operating Environment, Strategy and Outlook* — Beginning on page 57

  This section provides information about the following: Our Business; our performance during the third quarter and first nine months of 2018 and 2017; Our Operating Environment; The Global Economic Environment; Our Strategy; Our Business Development Initiatives, such as acquisitions, dispositions, licensing and collaborations; and Our Financial Guidance for 2018.
- *Significant Accounting Policies and Application of Critical Accounting Estimates and Assumptions* — Beginning on page 71

  This section discusses updates to our 2017 Financial Report disclosures for those accounting policies and estimates that we consider important in understanding our consolidated financial statements. For additional discussion of our accounting policies, see Notes to Consolidated Financial Statements— *Note 1. Basis of Presentation and Significant Accounting Policies* .
- *Analysis of the Condensed Consolidated Statements of Income* — Beginning on page 72

  This section includes the following sub-sections:
  - *Revenues by Segment and Geography* — Beginning on page 72

    This sub-section provides an overview of revenues by segment and geography as well as revenue deductions
  - *Revenues - Selected Product Discussion* — Beginning on page 76

    This sub-section provides an overview of several of our biopharmaceutical products.
  - *Product Developments - Biopharmaceutical* — Beginning on page 82

    This sub-section provides an overview of important biopharmaceutical product developments.
  - *Costs and Expenses* — Beginning on page 85

    This sub-section provides a discussion about our costs and expenses.
  - *Provision for Taxes on Income* — Beginning on page 88

    This sub-section provides a discussion of items impacting our tax provisions.
  - *Non-GAAP Financial Measure (Adjusted Income)* — Beginning on page 88

    This sub-section provides a discussion of an alternative view of performance used by management.
- *Analysis of Operating Segment Information* — Beginning on page 94

  This section provides a discussion of the performance of each of our operating segments.
- *Analysis of the Condensed Consolidated Statements of Comprehensive Income* — Beginning on page 102

  This section provides a discussion of changes in certain components of other comprehensive income.
- *Analysis of the Condensed Consolidated Balance Sheets* — Beginning on page 102

  This section provides a discussion of changes in certain balance sheet accounts.
- *Analysis of the Condensed Consolidated Statements of Cash Flows* — Beginning on page 104

  This section provides an analysis of our cash flows for the first nine months of 2018 and 2017.
- *Analysis of Financial Condition, Liquidity and Capital Resources* — Beginning on page 105

  This section provides an analysis of selected measures of our liquidity and of our capital resources as of September 30, 2018 and December 31, 2017, as well as a discussion of our outstanding debt and other commitments that existed as of September 30, 2018 and December 31, 2017. Included in the discussion of outstanding debt is a discussion of the amount of financial capacity available to help fund Pfizer's future activities.
- *New Accounting Standards* — Beginning on page 109

  This section discusses accounting standards that we have recently adopted, as well as those that recently have been issued, but not yet adopted.
- *Forward-Looking Information and Factors That May Affect Future Results* — Beginning on page 111

  This section provides a description of the risks and uncertainties that could cause actual results to differ materially from those discussed in forward-looking statements presented in this MD&A. Also included in this section is a discussion of legal proceedings and contingencies.

Certain amounts in our MD&A may not add due to rounding. All percentages have been calculated using unrounded amounts.

The following table provides the components of the condensed consolidated statements of income:

(MILLIONS OF DOLLARS, EXCEPT PER COMMON SHARE DATA)	Three Months Ended			Nine Months Ended		
	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
Revenues	$ 13,298	$ 13,168	1	$ 39,670	$ 38,843	2
Cost of sales [(a)]	2,694	2,844	(5)	8,173	7,972	3
% of revenues	20.3%	21.6%		20.6%	20.5%	
Selling, informational and administrative expenses [(a)]	3,494	3,504	—	10,448	10,249	2
% of revenues	26.3%	26.6%		26.3%	26.4%	
Research and development expenses [(a)]	2,008	1,865	8	5,549	5,367	3
% of revenues	15.1%	14.2%		14.0%	13.8%	
Amortization of intangible assets	1,253	1,177	6	3,640	3,571	2
% of revenues	9.4%	8.9%		9.2%	9.2%	
Restructuring charges and certain acquisition-related costs	85	114	(26)	172	267	(36)
% of revenues	0.6%	0.9%		0.4%	0.7%	
Other (income)/deductions—net	(414)	79	*	(1,143)	65	*
Income from continuing operations before provision for taxes on income	4,177	3,585	17	12,831	11,351	13
% of revenues	31.4%	27.2%		32.3%	29.2%	
Provision for taxes on income	66	727	(91)	1,270	2,287	(44)
Effective tax rate	1.6%	20.3%		9.9%	20.1%	
Income from continuing operations	4,111	2,858	44	11,562	9,064	28
% of revenues	30.9%	21.7%		29.1%	23.3%	
Discontinued operations—net of tax	11	—	*	10	1	*
Net income before allocation to noncontrolling interests	4,122	2,858	44	11,571	9,066	28
% of revenues	31.0%	21.7%		29.2%	23.3%	
Less: Net income attributable to noncontrolling interests	8	18	(53)	25	32	(22)
Net income attributable to Pfizer Inc.	$ 4,114	$ 2,840	45	$ 11,546	$ 9,034	28
% of revenues	30.9%	21.6%		29.1%	23.3%	
Earnings per common share—basic :						
Income from continuing operations attributable to Pfizer Inc. common shareholders	$ 0.70	$ 0.48	46	$ 1.96	$ 1.51	29
Net income attributable to Pfizer Inc. common shareholders	$ 0.70	$ 0.48	47	$ 1.96	$ 1.51	29
Earnings per common share—diluted :						
Income from continuing operations attributable to Pfizer Inc. common shareholders	$ 0.69	$ 0.47	46	$ 1.92	$ 1.49	29
Net income attributable to Pfizer Inc. common shareholders	$ 0.69	$ 0.47	46	$ 1.92	$ 1.49	29
Cash dividends paid per common share	$ 0.34	$ 0.32	6	$ 1.02	$ 0.96	6

* Calculation not meaningful or results are equal to or greater than 100%.

[(a)] Excludes amortization of intangible assets, except as disclosed in Notes to Condensed Consolidated Financial Statements— *Note 9A. Identifiable Intangible Assets and Goodwill: Identifiable Intangible Assets.*

OVERVIEW OF OUR PERFORMANCE, OPERATING ENVIRONMENT, STRATEGY AND OUTLOOK

Our Business

We apply science and our global resources to bring therapies to people that extend and significantly improve their lives through the discovery, development and manufacture of healthcare products. Our global portfolio includes medicines and vaccines, as well as many of the world's best-known consumer healthcare products. We work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. We collaborate with healthcare providers, governments and local communities to support and expand access to reliable, affordable healthcare around the world. Our revenues are derived from the sale of our products and, to a much lesser extent, from alliance agreements, under which we co-promote products discovered or developed by other companies or us (Alliance revenues).

We manage our commercial operations through two distinct business segments: Pfizer Innovative Health (IH) and Pfizer Essential Health (EH). For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 13A. Segment, Geographic and Other Revenue Information : Segment Information* and the "Our Strategy — Commercial Operations" section of this MD&A below, including a discussion of our plans to reorganize our operations into three businesses effective at the beginning of fiscal 2019.

In October 2018, we announced our Board of Directors unanimously elected Dr. Albert Bourla, Pfizer Chief Operating Officer, to succeed Ian Read as Chief Executive Officer effective January 1, 2019. Ian Read will transition from his current role as Chairman and Chief Executive Officer to Executive Chairman of Pfizer's Board of Directors.

The majority of our revenues come from the manufacture and sale of biopharmaceutical products. As explained more fully in our 2017 Form 10-K, the biopharmaceutical industry is highly competitive and highly regulated. As a result, we face a number of industry-specific factors and challenges, which can significantly impact our results. These factors include, among others: the loss or expiration of intellectual property rights and the expiration of co-promotion and licensing rights, the ability to replenish innovative biopharmaceutical products, healthcare legislation, pipeline productivity, the regulatory environment, pricing and access pressures and competition. We also face challenges as a result of the global economic environment. For additional information about these factors and challenges, see the "Our Operating Environment" and "The Global Economic Environment" sections of this MD&A and of our 2017 Financial Report, Part I, Item 1A, "Risk Factors" of our 2017 Form 10-K and Part II, Item 1A, "Risk Factors" of this Quarterly Report on Form 10-Q.

The financial information included in our condensed consolidated financial statements for our subsidiaries operating outside the U.S. is as of and for the three and nine months ended August 26, 2018 and August 27, 2017 . The financial information included in our condensed consolidated financial statements for U.S. subsidiaries is as of and for the three and nine months ended September 30, 2018 and October 1, 2017 .

References to developed and emerging markets in this MD&A include:

Developed markets	U.S., Western Europe, Japan, Canada, Australia, South Korea, Scandinavian countries, Finland and New Zealand
Emerging markets (includes, but is not limited to)	Asia (excluding Japan and South Korea), Latin America, Eastern Europe, Africa, the Middle East, Central Europe and Turkey

References to operational variances in this MD&A pertain to period-over-period growth rates that exclude the impact of foreign exchange. The operational variances are determined by multiplying or dividing, as appropriate, our current period U.S. dollar results by the current period average foreign exchange rates and then multiplying or dividing, as appropriate, those amounts by the prior-year period average foreign exchange rates. Although exchange rate changes are part of our business, they are not within our control. Exchange rate changes, however, can mask positive or negative trends in the business; therefore, we believe presenting operational variances provides useful information in evaluating the results of our business.

On December 22, 2017, the U.S. enacted significant changes to U.S. tax law following the passage and signing of the TCJA. The TCJA is complex and significantly changes the U.S. corporate income tax system by, among other things, reducing the U.S. Federal corporate tax rate from 35% to 21%, transitioning U.S. international taxation from a worldwide tax system to a territorial tax system and imposing a repatriation tax on deemed repatriated accumulated post-1986 earnings of foreign subsidiaries. For information on estimates and assumptions in connection with the TCJA, see Notes to Condensed Consolidated Financial Statements— *Note 5A. Tax Matters: Taxes on Income from Continuing Operations.*

We continue to review strategic options for our Consumer Healthcare business. We remain disciplined regarding our capital allocation, and at this time we have not received an acceptable offer for the sale of this business. We will continue our

management of this strong business as we explore other alternatives, which could include everything from a full or partial separation of the business to ultimately deciding to retain the business. We continue to expect that any decision regarding strategic alternatives for our Consumer Healthcare business will be made during the fourth quarter of 2018.

Our other significant business development activities include:

- On February 3, 2017, we completed the sale of Pfizer's global infusion systems net assets, HIS, to ICU Medical for up to approximately $900 million, composed of cash and contingent cash consideration, ICU Medical common stock and seller financing. At closing, we received 3.2 million newly issued shares of ICU Medical common stock, which we initially valued at approximately $428 million (a portion of which we sold in August 2018), a promissory note in the amount of $75 million and net cash of approximately $200 million before customary adjustments for net working capital. In addition, we are entitled to receive a contingent amount of up to an additional $225 million in cash based on ICU Medical's achievement of certain cumulative performance targets for the combined company through December 31, 2019. The operating results of HIS are included in our condensed consolidated statement of income and EH's operating results through February 2, 2017 and, therefore, our financial results, and EH's operating results, for the third quarter of 2017 do not reflect any contribution from HIS global operations, while our financial results, and EH's operating results, for the first nine months of 2017 reflect approximately one month of HIS domestic operations and approximately two months of HIS international operations. Our financial results, and EH's operating results, for 2018 do not reflect any contribution from HIS global operations.
- On December 22, 2016, which falls in the first fiscal quarter of 2017 for our international operations, we acquired the development and commercialization rights to AstraZeneca's small molecule anti-infectives business, primarily outside the U.S. for $1,040 million , composed of cash and contingent consideration. Commencing from the acquisition date, our financial statements reflect the assets, liabilities, operating results and cash flows of this business, and, in accordance with our international reporting period, our financial results, EH's operating results, and cash flows for the third quarter and first nine months of 2017 reflect approximately three months and eight months, respectively, of the small molecule anti-infectives business acquired from AstraZeneca. Our financial results, EH's operating results, and cash flows for the third quarter and first nine months of 2018 reflect three months and nine months, respectively, of the small molecule anti-infective business acquired from AstraZeneca.

For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 2. Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment* and the "Our Strategy" and "Our Business Development Initiatives" sections of this MD&A below.

Impact of Hurricanes in Puerto Rico

We have manufacturing and commercial operations in Puerto Rico, which were impacted by the hurricanes toward the end of the third quarter in 2017. While our three manufacturing sites sustained some damage and became inoperable due to issues impacting Puerto Rico overall, all three sites have resumed operations and remediation activities will continue through the remainder of the year. Given prior inoperability along with ongoing remediation of our sites, there could be certain product shortages in the coming months. Our commercial sales offices in Puerto Rico have been operational since October 2017.

Product Manufacturing

We periodically encounter difficulties or delays in manufacturing, including due to suspension of manufacturing or voluntary recall of a product, or legal or regulatory actions such as warning letters. The product shortages we have been experiencing within our Essential Health portfolio are primarily for products from the legacy Hospira portfolio and are largely driven by capacity constraints, technical issues and supplier quality concerns. We continue to remediate issues at legacy Hospira facilities manufacturing sterile injectables within our Essential Health portfolio. Any continuing product shortage interruption at these manufacturing facilities could negatively impact our financial results, specifically in our SIP portfolio. We continue to make progress on our comprehensive remediation plan to upgrade and modernize these facilities, and we expect our supply issues to be significantly improved by the end of 2019.

Our 2018 Performance

Revenues

Revenues in the third quarter of 2018 increase d $130 million , or 1% , compared to the same period in 2017 , which reflects an operational increase of $243 million , or 2% , partially offset by the unfavorable impact of foreign exchange of $113 million , or 1% . *Revenues* in the first nine months of 2018 increase d $827 million , or 2% , compared to the same period in 2017 , which reflects a favorable impact of foreign exchange of $693 million , or 2% , and an operational increase of $134 million .

The following provides an analysis of the changes in revenues for the third quarter and first nine months of 2018 :

(MILLIONS OF DOLLARS)	Three Months	Nine Months
Revenues, for the three and nine months ended October 1, 2017	$ 13,168	$ 38,843
Operational growth/(decline):		
Continued growth from key brands [(a)] and from recently launched products [(b)], as well as growth from Biosimilars [(c)]	768	2,172
Declines from the SIP portfolio (primarily in the U.S.), the Peri-LOE Products portfolio (excluding Viagra EH [(d)], which was impacted by the shift in the reporting of U.S. and Canada Viagra revenues to EH), total Viagra [(d)] (primarily in the U.S.), Enbrel (driven by declines in most developed Europe markets) and the LEP portfolio (primarily in developed markets)	(508)	(1,971)
Disposition-related impact of the February 2017 sale of HIS [(e)]	—	(97)
Other operational factors, net	(18)	29
Operational growth, net	243	134
Operational revenues	13,410	38,977
(Unfavorable)/favorable impact of foreign exchange	(113)	693
Revenues, for the three and nine months ended September 30, 2018	$ 13,298	$ 39,670

[(a)] K ey brands represent Eliquis, Ibrance, Xeljanz, Prevnar 13/Prevenar 13 and Xtandi, as well as, for the first nine months of 2018, Chantix/Champix.
[(b)] Growth from recently launched products include Eucrisa in the U.S., as well as Besponsa and Bavencio, primarily in the U.S. and developed Europe.
[(c)] Growth from Biosimilars, primarily from Inflectra in certain channels in the U.S., as well as in developed Europe.
[(d)] Viagra lost exclusivity in the U.S. in December 2017. Beginning in 2018, revenues for Viagra in the U.S. and Canada, which were reported in IH through 2017, are reported in EH (which reported all other Viagra revenues excluding the U.S. and Canada through 2017). Therefore, beginning in 2018, total Viagra revenues are reported in EH. Total Viagra revenues in 2017 represent the aggregate of worldwide revenues from Viagra IH and Viagra EH.
[(e)] Impact on financial results for the sale of HIS in February 2017. The first nine months of 2018 do not reflect any contribution from HIS global operations, compared to approximately one month of HIS domestic operations and approximately two months of HIS international operations in the same period in 2017 .

For worldwide revenues, by geography, for selected products, see the discussion in the "Analysis of the Condensed Consolidated Statements of Income—Revenues and Product Developments—Revenues—Selected Product Discussion" section of this MD&A. For additional information regarding the primary indications or class of certain products, see Notes to Condensed Consolidated Financial Statements— *Note 13C. Segment, Geographic and Other Revenue Information* : *Other Revenue Information* .

See the "Analysis of the Condensed Consolidated Statements of Income—Revenues and Product Developments—Revenues by Segment and Geography" section below for more information, including a discussion of key drivers of our revenue performance.

Income from Continuing Operations Before Provision for Taxes on Income

The following provides an analysis of the increase in *Income from continuing operations before provision for taxes on income* for the third quarter and first nine months of 2018 :

(MILLIONS OF DOLLARS)	Three Months	Nine Months
Income from continuing operations before provision for taxes on income, for the three and nine months ended October 1, 2017	$ 3,585	$ 11,351
Favorable change in revenues	130	827
Favorable/(unfavorable) changes:		
Higher net gains recognized during the period on investments in equity securities [a]	49	349
Impact of net periodic benefit costs/(credits) other than service costs [a]	93	313
Higher income from collaborations, out-licensing arrangements and sales of compound/product rights [a]	61	292
Impact of certain legal matters, net [a]	146	264
Lower certain asset impairments [a]	131	103
Impact of *Cost of sales* [b]	149	(202)
Impact of *Selling, information and administrative expenses* [c]	10	(198)
Higher *Research and development expenses* [d]	(144)	(182)
Higher *Amortization of intangible assets* [e]	(76)	(69)
All other items, net	43	(17)
Income from continuing operations before provision for taxes on income, for the three and nine months ended September 30, 2018	$ 4,177	$ 12,831

[a] See the Notes to Condensed Consolidated Financial Statements— *Note 4. Other (Income)/Deductions—Net* .
[b] See the "Costs and Expenses—Cost of Sales" section of this MD&A.
[c] See the "Costs and Expenses—Selling, Informational and Administrative (SI&A) Expenses" section of this MD&A.
[d] See the "Costs and Expenses—Research and Development (R&D) Expenses" section of this MD&A.
[e] See the "Costs and Expenses—Amortization of Intangible Assets" section of this MD&A.

For information on our tax provision and effective tax rate see the "Provision for Taxes on Income" section of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 5 . Tax Matters* .

Our Operating Environment

Industry-Specific Challenges

Intellectual Property Rights and Collaboration/Licensing Rights

The loss, expiration or invalidation of intellectual property rights, patent litigation settlements with generic manufacturers and the expiration of co-promotion and licensing rights can have a significant adverse effect on our revenues. Many of our branded products have multiple patents that expire at varying dates, thereby strengthening our overall patent protection. However, once patent protection has expired or has been lost prior to the expiration date as a result of a legal challenge, we lose exclusivity on these products, and generic pharmaceutical manufacturers generally produce similar products and sell them for a lower price. The date at which generic competition commences may be different from the date that the patent or regulatory exclusivity expires. However, when generic competition does commence, the resulting price competition can substantially decrease our revenues for the impacted products, often in a very short period of time. Also, if one of our patents is found to be invalid by judicial, court or administrative proceedings, such as inter partes review, post-grant review, re-examination or opposition proceedings, before the U.S. Patent and Trademark Office, the European Patent Office, or other foreign counterparts, generic or competitive products could be introduced into the market resulting in the erosion of sales of our existing products. For example, several of the patents in our pneumococcal vaccine portfolio were challenged in inter partes review and post-grant review proceedings in the U.S. In June 2018, the Patent Trial and Appeal Board ruled on one patent, holding that one claim was valid and that all other claims were invalid. The party challenging that patent has appealed the decision. Challenges to other patents remain pending before the U.S. Patent and Trademark Office. The invalidation of these patents could potentially allow a competitor pneumococcal vaccine into the marketplace.

As a result of a patent litigation settlement, Teva Pharmaceuticals USA, Inc. launched a generic version of Viagra in the U.S. in December 2017. See the "Intellectual Property Rights and Collaboration/Licensing Rights" section of our 2017 Financial Report for additional information about (i) recent losses and expected losses of product exclusivity in the U.S., Europe and/or Japan impacting product revenues and (ii) recent losses of collaboration rights impacting alliance revenues.

We lost or expect to lose exclusivity for various other products in various markets over the next few years, including, among others, the expiration of the basic product patent for Lyrica in the U.S. in December 2018. Pfizer is currently pursuing a six-month patent-term extension for pediatric exclusivity for Lyrica in the U.S. with the FDA.

For additional information, see the "Patents and Other Intellectual Property Rights" section in Part I, Item 1, "Business" of our 2017 Form 10-K.

We will continue to aggressively defend our patent rights whenever we deem appropriate. For a discussion of certain recent developments with respect to patent litigation, see Notes to Condensed Consolidated Financial Statements— *Note 12A1. Contingencies and Certain Commitments : Legal Proceedings — Patent Litigation* .

Regulatory Environment/Pricing and Access—U.S. Healthcare Legislation

In March 2010, the ACA was enacted in the U.S. For additional information, see the "Government Regulation and Price Constraints" section in Part I, Item 1, "Business" of our 2017 Form 10-K.

We recorded the following amounts as a result of the U.S. Healthcare Legislation:

	Three Months Ended		Nine Months Ended	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Reduction to *Revenues* , related to the Medicare "coverage gap" discount provision	$ 217	$ 157	$ 435	$ 296
Selling, informational and administrative expenses , related to the fee payable to the federal government (which is not deductible for U.S. income tax purposes), based on our prior-calendar-year share relative to other companies of branded prescription drug sales to specified government programs. The first nine months of 2018 also reflected a favorable true-up associated with the updated 2017 invoice received from the federal government, which reflected a lower expense than what was previously estimated for invoiced periods.	43	87	118	218

Regulatory Environment/Pricing and Access—Government and Other Payer Group Pressures

The pricing of medicines by pharmaceutical manufacturers and the cost of healthcare, which includes medicines, medical services and hospital services, continues to be important to payers, governments, patients, and other stakeholders. We believe that medicines are amongst the most powerful tool for patients in curing, treating and preventing illness and disability, and that all patients should have appropriate access to the medicines their doctors prescribe. We may consider a number of factors when determining a medicine's price, including, for example, its impact on patients and their disease, other available treatments, the medicine's potential to reduce other healthcare costs (such as hospital stays), and affordability. Within the U.S., in particular, we may also engage with patients, doctors and healthcare plans regarding their views. We also negotiate with insurers, including PBMs and MCOs, often providing significant discounts to them from the initial price. The price that patients pay in the U.S. for the medicines their physicians prescribe is ultimately set by healthcare providers and insurers. On average, in the U.S., insurers cover a much lower share of prescription drug costs than medical services, which results in a greater proportion of out-of-pocket costs being passed on to patients for medicines, thereby making them less accessible and affordable. We will continue to work with insurance providers, governments and others to improve access to today's innovative treatments.

Governments, MCOs and other payer groups continue to seek increasing discounts on our products through a variety of means, such as leveraging their purchasing power, implementing price controls, and demanding price cuts (directly or by rebate actions). In Europe, Japan, China, Canada, South Korea and some other international markets, governments provide healthcare at low-to-zero direct cost to consumers at the point of care and have significant power as large single payers to regulate pharmaceutical prices or patient reimbursement levels to control costs for the government-sponsored healthcare system, particularly under recent global economic pressures. In the U.S., government action to reduce federal spending on entitlement programs including Medicare and Medicaid may affect payment for our products or services provided using our products. Any significant spending reductions or cost controls affecting Medicare, Medicaid or other publicly funded or subsidized health programs that may be implemented could have an adverse impact on our results of operations. Significant Medicare reductions could also result if Congress proceeds with certain proposals to convert the Medicare fee-for-service program into a premium support program, or Congress chooses to implement the recommendations made annually by the Medicare Payment Advisory Commission, which are primarily intended to extend the fiscal solvency of the Medicare program.

Consolidation among MCOs has increased the negotiating power of MCOs and other private insurers. Private third-party insurers, as well as governments, increasingly employ formularies to control costs by negotiating discounted prices in exchange

for formulary inclusion. Failure to obtain or maintain timely or adequate pricing or formulary placement for our products or obtaining such pricing or placement at unfavorable pricing could adversely impact revenue.

Efforts by government officials or legislators to implement measures to regulate prices or payment for pharmaceutical products, including legislation on drug importation, could adversely affect our business if implemented. Recently, there has been considerable public and government scrutiny of pharmaceutical pricing and proposals to address the perceived high cost of pharmaceuticals. There have also been state legislative efforts to address drug costs, which generally have focused on increasing transparency around drug costs or limiting drug prices. Certain state legislation has been subject to legal challenges.

Adoption of new legislation at the federal or state level could further affect demand for, or pricing of, our products. We believe medicines are the most efficient and effective use of healthcare dollars based on the value they deliver to the overall healthcare system. We will continue to work with law makers and advocate for solutions that effectively improve patient health outcomes, lower costs to the healthcare system, and ensure access to medicines within an efficient and affordable healthcare system.

We face uncertainties due to federal legislative and administrative efforts to repeal, substantially modify or invalidate some or all of the provisions of the ACA. The likelihood of such a repeal currently appears low given the recent U.S. midterm elections, which resulted in Democratic control of the House of Representatives. Although the revenues generated for Pfizer by the health insurance exchanges under the ACA are minor, there is no assurance that any future replacement, modification or repeal of the ACA will not adversely affect our business and financial results, particularly if the legislation reduces incentives for employer-sponsored insurance coverage. We also may face uncertainties if our industry is looked to for savings to fund certain legislation, such as lifting the debt ceiling. One recent example is the Bipartisan Budget Act of 2018, which increased the discount we pay in the Medicare Part D “coverage gap” from 50% to 70%, which will modestly reduce our future Medicare Part D revenues.

In May 2018, President Trump released his *Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs* (Blueprint). Pfizer communicated a formal response to the request for information that accompanied the Blueprint, and is participating in the subsequent rule-making process to advance the proposals that are most likely to bring meaningful out-of-pocket cost relief to patients. Certain proposals in the Blueprint, and related drug pricing measures proposed since the Blueprint, could cause significant operational and reimbursement changes for the pharmaceutical industry. On July 10, 2018, Pfizer decided to defer price increases that were effective July 1, 2018, and return those prices to their pre-July 1, 2018 levels. In addition, the price declines that we took as of July 1, 2018 remain in effect.

The potential for additional pricing and access pressures in the commercial sector continues to be significant. Some employers, seeking to avoid the tax on high-cost health insurance in the ACA to be imposed in 2022, are already scaling back healthcare benefits and an increasing number are implementing high deductible benefit designs. This is a trend that is likely to continue. Private third-party payers, such as health plans, increasingly challenge pharmaceutical product pricing, which could result in lower prices, lower reimbursement rates and a reduction in demand for our products. Pricing pressures for our products may occur as a result of highly competitive insurance markets. Healthcare provider purchasers, directly or through group purchasing organizations, are seeking enhanced discounts or implementing more rigorous bidding or purchasing review processes.

Overall, there is increasing pressure on U.S. providers to deliver healthcare at a lower cost and to ensure that those expenditures deliver demonstrated value in terms of health outcomes. Longer term, we are seeing a shift in focus away from fee-for-service payments towards outcomes-based payments and risk-sharing arrangements that reward providers for cost reductions. These new payment models can, at times, lead to lower prices for, and restricted access to, new medicines. At the same time, these models can also expand utilization by encouraging physicians to screen, diagnose and focus on outcomes.

Outside the U.S., governments, including the different EU Member States, Japan and Canada, may use a variety of cost-containment measures for our pharmaceutical products, including price cuts, mandatory rebates, health technology assessments, forced localization as a condition of market access and international reference pricing (i.e., the practice of a country linking its regulated medicine prices to those of other countries). This international patchwork of price regulation and differing economic conditions and incomplete value assessments across countries has led to different prices in different countries, varying health outcomes and some third-party trade in our products between countries.

In particular, international reference pricing adds to the regional impact of price cuts in individual countries and hinders patient access and innovation. Price variations, exacerbated by international reference pricing systems, also have resulted from exchange rate fluctuations. The downward pricing pressure resulting from this dynamic can be expected to continue as a result of reforms to international reference pricing policies and measures targeting pharmaceuticals in some European countries.

In addition, several important multilateral organizations, such as the United Nations (UN) and the Organization for Economic Cooperation and Development (OECD), are increasing scrutiny of international pharmaceutical pricing through issuing reports and policy recommendations (e.g., *2016 UN High Level Panel Report on Access to Medicines* and *2017 OECD Report on New Health Technologies—Managing Access, Value and Sustainability*). The recommendations from these reports and any other recommendations that may be made in the future will continue to exert additional pricing pressures.

In response to the evolving U.S. and global healthcare spending landscape, we are continuing to work with health authorities, health technology assessment and quality measurement bodies and major U.S. payers throughout the product-development process to better understand how these entities value our compounds and products. Further, we are seeking to develop stronger internal capabilities focused on demonstrating the value of the medicines that we discover or develop, register and manufacture, by recognizing patterns of usage of our medicines and competitor medicines along with patterns of healthcare costs.

For additional information, see the "Regulatory Environment—Pipeline Productivity" and "Competition" sections of our 2017 Financial Report.

The Global Economic Environment

In addition to the industry-specific factors discussed above, we, like other businesses, are exposed to the economic cycle, which impacts our biopharmaceutical operations globally.

- Governments, corporations, and insurance companies, which provide insurance benefits to patients, have implemented increases in cost-sharing and restrictions on access to medicines, potentially causing patients to switch to generic or biosimilar products, delay treatments, skip doses or use less effective treatments. Government financing pressures can lead to negative pricing pressure in various markets where governments take an active role in setting prices, access criteria (e.g., through public or private health technology assessments), or other means of cost control. Examples include Europe, Japan, China, Canada, South Korea and a number of other international markets. The U.S. continues to maintain competitive insurance markets, but has also seen significant increases in patient cost-sharing and growing government influence as government programs continue to grow as a source of coverage.
- Significant portions of our revenues, costs and expenses, as well as our substantial international net assets, are exposed to changes in foreign exchange rates. We seek to manage our foreign exchange risk in part through operational means, including managing same-currency revenues in relation to same-currency costs and same-currency assets in relation to same-currency liabilities. Depending on market conditions, foreign exchange risk also is managed through the use of derivative financial instruments and foreign currency debt. As we operate in multiple foreign currencies, including the euro, the Japanese yen, the Chinese renminbi, the U.K. pound, the Canadian dollar and approximately 100 other currencies, changes in those currencies relative to the U.S. dollar will impact our revenues and expenses. If the U.S. dollar were to weaken against another currency, assuming all other variables remained constant, our revenues would increase, having a positive impact on earnings, and our overall expenses would increase, having a negative impact on earnings. Conversely, if the U.S. dollar were to strengthen against another currency, assuming all other variables remained constant, our revenues would decrease, having a negative impact on earnings, and our overall expenses would decrease, having a positive impact on earnings. Therefore, significant changes in foreign exchange rates can impact our results and our financial guidance.

  The impact of possible currency devaluations in countries experiencing high inflation rates or significant exchange fluctuations, including Venezuela and Argentina, can impact our results and financial guidance. For further information about our exposure to foreign currency risk, see the "Analysis of Financial Condition, Liquidity and Capital Resources" and the "Our Financial Guidance for 2018 " sections of this MD&A.
- In June 2016, the U.K. electorate voted in a referendum to leave the EU, which is commonly referred to as "Brexit". In March 2017, the U.K. government formally notified the European Council of its intention to leave the EU after it triggered Article 50 of the Lisbon Treaty to begin the two-year negotiation process establishing the terms of the exit and outlining the future relationship between the U.K. and the EU. Formal negotiations officially started in June 2017. This process continues to be highly complex and the end result of these negotiations may pose certain implications to our research, commercial and general business operations in the U.K. and the EU, including the approval and supply of our products. The EMA announced in November 2017 that it will be relocating from London, U.K. to Amsterdam, Netherlands by the expected date of Brexit in March 2019.

  We generated approximately 2% of our worldwide revenues from the U.K. in 2017 and in the first nine months of 2018 , including the foreign currency exchange impact from the weakening U.K. pound relative to the U.S. dollar to date. We recognize that there are still significant uncertainties surrounding the ultimate resolution of Brexit negotiations, and we will continue to monitor any changes that may arise and assess their potential impact on our business.

  Pfizer's preparations are well advanced to make the changes necessary to meet EU legal requirements after the U.K. is no longer a member state, especially in the regulatory, manufacturing and supply chain areas. The aim is to ensure the continuity of supply to patients in Europe (EU and U.K.) and other global markets impacted by these changes. The one-time costs of making these adaptations are currently estimated at approximately $100 million.
- On December 22, 2017, the U.S. enacted significant changes to U.S. tax law following the passage and signing of the TCJA. The TCJA is complex and significantly changes the U.S. corporate income tax system by, among other things, reducing the U.S. Federal corporate tax rate from 35% to 21%, transitioning U.S. international taxation from a worldwide tax system to a

territorial tax system and imposing a repatriation tax on deemed repatriated accumulated post-1986 earnings of foreign subsidiaries. Given the significant changes resulting from and complexities associated with the TCJA, the estimated financial impacts for 2017, as well as the estimated impact on 2018 financial guidance for the effective tax rate on adjusted income remain provisional and subject to further analysis, interpretation and clarification of the TCJA, which could result in further changes to these estimates during the fourth quarter of 2018. For additional information, see the "Our Financial Guidance for 2018 ", "Provision for Taxes on Income" and "Analysis of Financial Condition, Liquidity and Capital Resources" sections of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 5A. Tax Matters: Taxes on Income from Continuing Operations.*

Pfizer maintains a strong financial position while operating in a complex global environment. Due to our significant operating cash flows, financial assets, access to capital markets and available lines of credit and revolving credit agreements, we continue to believe that we have, and will maintain, the ability to meet our liquidity needs for the foreseeable future. Our long-term debt is rated high quality by both S&P and Moody's. As market conditions change, we continue to monitor our liquidity position. We have taken and will continue to take a conservative approach to our financial investments. Both short-term and long-term investments consist primarily of high-quality, highly liquid, well-diversified, available-for-sale debt securities. For further discussion of our financial condition and credit ratings, see the "Analysis of Financial Condition, Liquidity and Capital Resources" section of this MD&A.

These and other industry-wide factors that may affect our businesses should be considered along with information presented in the "Forward-Looking Information and Factors That May Affect Future Results" section of this MD&A and in Part I, Item 1A, "Risk Factors" of our 2017 Form 10-K and Part II, Item 1A, "Risk Factors" of this Quarterly Report on Form 10-Q.

Our Strategy

We believe that our medicines provide significant value for both healthcare providers and patients, not only from the improved treatment of diseases but also from a reduction in other healthcare costs, such as emergency room or hospitalization costs, as well as improvements in health, wellness and productivity. We continue to actively engage in dialogues about the value of our medicines and how we can best work with patients, physicians and payers to prevent and treat disease and improve outcomes. We continue to work within the current legal and pricing structures, as well as continue to review our pricing arrangements and contracting methods with payers, to maximize patient access and minimize any adverse impact on our revenues. We remain firmly committed to fulfilling our company ' s purpose of innovating to bring therapies to patients that extend and significantly improve their lives. By doing so, we expect to create value for the patients we serve and for our shareholders.

Organizing for Growth

We expect higher and more sustained growth post-2020 after our near-term patent expirations occur. Therefore, in July 2018, we announced that we will organize our company into three businesses effective at the beginning of our 2019 fiscal year. We believe the new structure better positions each business to achieve its growth potential:

- a science-based Innovative Medicines business, which will include all of our current Innovative Health medicines and vaccines business units as well as biosimilars and a new Hospital Medicines business unit that will commercialize our global portfolio of sterile injectable and anti-infective medicines;
- an off-patent branded and generic Established Medicines business; and
- a Consumer Healthcare business, for which we continue to evaluate strategic alternatives, with a decision expected in the fourth quarter of 2018.

These changes will not be effective until the beginning of our 2019 fiscal year to allow for the necessary internal transition process. We are currently evaluating the impact to our operating segments and other costs and activities based on how the businesses will be managed in 2019. Beginning with our first-quarter 2019 financial results, our financial reporting will reflect the new organizational structure.

As we prepare for expected growth, we are focused on creating a simpler, more efficient structure within each business and the functions that support them. Further, as our innovative pipeline matures with the anticipated progression of current and the initiation of new pivotal trials, we will need to increase our R&D investments. In addition, as our pipeline potentially delivers new commercialization opportunities, we will need to increase our investments in new-market-creation activities.

To partially offset these incremental cost increases, we expect to generate cost reduction opportunities, particularly in SI&A. We are taking steps to simplify the organization, increase spans of control and reduce organizational layers. As such, we expect some managerial roles and responsibilities to be impacted. Enhancements to certain employee benefits are being offered for a short period of time. We do not yet know the impact of these voluntary and involuntary plans, but expect to record a special termination benefit as well as severance in the fourth quarter of 2018. Such benefits will be reflected as Certain Significant Items and excluded from our non-GAAP measure of Adjusted Income. We do not expect the expenses related to these

enhancements to change our current full year 2018 guidance. Any future impact will be considered in the totality of our annual guidance for 2019.

Commercial Operations

We currently manage our commercial operations through two distinct business segments: Pfizer Innovative Health (IH) and Pfizer Essential Health (EH). The IH and EH operating segments are each led by a single manager. Each operating segment has responsibility for its commercial activities and for certain IPR&D projects for new investigational products and additional indications for in-line products that generally have achieved proof-of-concept. Each business has a geographic footprint across developed and emerging markets.

Some additional information about our business segments as of September 30, 2018 follows:

Pfizer Innovative Health	Pfizer ESSENTIAL HEALTH
• IH focuses on developing and commercializing novel, value-creating medicines and vaccines that significantly improve patients' lives, as well as products for consumer healthcare. Key therapeutic areas include internal medicine, vaccines, oncology, inflammation & immunology, rare disease and consumer healthcare.	• EH includes legacy brands that have lost or will soon lose market exclusivity in both developed and emerging markets, branded and generic sterile injectable products, biosimilars, and select branded products including anti-infectives. EH also includes an R&D organization, as well as our contract manufacturing business. Through February 2, 2017, EH also included HIS.
• We expect that the IH biopharmaceutical portfolio of innovative, largely patent-protected, in-line and newly launched products will be sustained by ongoing investments to develop promising assets and targeted business development in areas of focus to help ensure a pipeline of highly-differentiated product candidates in areas of unmet medical need. The assets managed by IH are science-driven, highly differentiated and generally require a high-level of engagement with healthcare providers and consumers.	• EH is expected to generate strong consistent cash flow by providing patients around the world with access to effective, lower-cost, high-value treatments. EH leverages our biologic development, regulatory and manufacturing expertise to seek to advance its biosimilar development portfolio. Additionally, EH leverages capabilities in formulation development and manufacturing expertise to help advance its generic sterile injectables portfolio. EH may also engage in targeted business development to further enable its commercial strategies.
• IH will have continued focus on R&D productivity and pipeline strength while maximizing the value of our recently launched brands and in-line portfolio. We have also expanded our pipeline in high priority therapeutic areas such as inflammation and immunology and oncology with select business development transactions.	• For EH, we continue to invest in growth drivers and manage the portfolio to extract additional value while seeking opportunities for operating efficiencies. This strategy includes active management of our portfolio; maximizing growth of core product segments; acquisitions to strengthen core areas of our portfolio further, such as our acquisition of AstraZeneca's small molecule anti-infectives business; and divestitures to increase focus on our core strengths. In line with this strategy, on February 3, 2017, we completed the sale of Pfizer's global infusion systems net assets, representing the infusion systems net assets that we acquired as part of the Hospira transaction, HIS, to ICU Medical.
Leading brands include: - *Prevnar 13/Prevenar 13* - *Xeljanz* - *Eliquis* - *Lyrica* (U.S., Japan and certain other markets) - *Enbrel* (outside the U.S. and Canada) - *Ibrance* - *Xtandi* - Several OTC consumer healthcare products (e.g., *Advil* and *Centrum*)	**Leading brands include:** - *Lipitor* - *Norvasc* - *Lyrica* (Europe, Russia, Turkey, Israel and Central Asia countries) - *Celebrex* - *Viagra** - *Inflectra/Remsima* - *Sulperazon* - Several other sterile injectable products

* Viagra lost exclusivity in the U.S. in December 2017. Beginning in 2018, revenues for Viagra in the U.S. and Canada, which were reported in IH through 2017, are reported in EH (which reported all other Viagra revenues excluding the U.S. and Canada through 2017). Therefore, beginning in 2018, total Viagra worldwide revenues are reported in EH.

For additional information about the 2018 performance for each of our operating segments, see the "Analysis of Operating Segment Information" section of this MD&A.

Description of Research and Development Operations

The following description of R&D operations reflects operations as of September 30, 2018.

Innovation is critical to the success of our company, and drug discovery and development is time-consuming, expensive and unpredictable. Our goal is to discover, develop and bring to market innovative products that address major unmet medical needs. Our R&D priorities include:

- delivering a pipeline of differentiated therapies and vaccines with the greatest medical and commercial potential;
- advancing our capabilities that can position Pfizer for long-term leadership; and
- creating new models for biomedical collaboration that will expedite the pace of innovation and productivity.

To that end, our R&D primarily focuses on:

- Biosimilars;
- Inflammation and Immunology;
- Internal Medicine;
- Oncology;
- Rare Diseases; and
- Vaccines.

In January 2018, we announced our decision to end internal neuroscience discovery and early development efforts and re-allocate funding to other areas where we have stronger scientific leadership. The development of tanezumab and potential treatments for rare neuromuscular disorders is not impacted by this decision. In June 2018, we announced our plan to invest $600 million in biotechnology and other emerging growth companies through Pfizer Ventures, our venture investment vehicle. Pfizer Ventures will seek to invest approximately 25% of its available capital ($150 million) in promising early-stage neuroscience companies. In addition to increased funding, we will extend our leadership as a venture capital investor with an expanded team that leverages expertise across venture capital investing, business development, drug discovery and clinical development. The new organization consolidates R&D Innovate, Pfizer's R&D equity investment vehicle, with Pfizer Venture Investments, our long-standing venture investment group. In September 2018, we and Bain Capital entered into a transaction to create a new biopharmaceutical company, Cerevel, to continue development of a portfolio of clinical and preclinical stage neuroscience assets primarily targeting disorders of the central nervous system including Parkinson's disease, epilepsy, Alzheimer's disease, schizophrenia and addiction. For additional information on the transaction with Bain Capital, see the Notes to Condensed Consolidated Financial Statements— *Note 2B.* Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment *: Divestitures* .

We continue to strengthen our global R&D organization and pursue strategies intended to improve innovation and overall productivity in R&D to achieve a sustainable pipeline that will deliver value in the near term and over time. Our R&D spending is conducted through a number of matrix organizations:

- Research Units within our WRD organization are generally responsible for research and early-stage development assets for our IH business (assets that have not yet achieved proof-of-concept). Our Research Units are organized by therapeutic area to enhance flexibility, cohesiveness and focus. Because of our structure, we can rapidly redeploy resources within a Research Unit between various projects as necessary because the workforce shares similar skills, expertise and/or focus.
- Our R&D organization within the EH business supports the large base of EH products and is expected to develop potential new sterile injectable drugs and therapeutic solutions, as well as biosimilars.
- Our GPD organization is a unified center for late-stage development for our innovative products and is generally responsible for the operational execution of clinical development of assets that are in clinical trials for our WRD and Innovative portfolios. GPD is expected to enable more efficient and effective development and enhance our ability to accelerate and progress assets through our pipeline.
- Our science-based and other platform-services organizations, where a significant portion of our R&D spending occurs, provide technical expertise and other services to the various R&D projects, and are organized into science-based functions (which are part of our WRD organization), such as Pharmaceutical Sciences, Medicinal Chemistry, Regulatory and Drug Safety, and non-science-based functions, such as Facilities, Business Technology and Finance. As a result, within each of these functions, we are able to migrate resources among projects, candidates and/or targets in any therapeutic area and in most phases of development, allowing us to react quickly in response to evolving needs.

We manage R&D operations on a total-company basis through our matrix organizations described above. Specifically, a single committee with representation from the R&D groups and the IH commercial organization is accountable for aligning resources among all of our WRD, GPD and IH R&D projects and for seeking to ensure optimal capital allocation across the Innovative

R&D portfolio. We believe that this approach also serves to maximize accountability and flexibility. Our EH R&D organization manages its resources separately from the WRD and GPD organizations.

Generally, we do not disaggregate total R&D expense by development phase or by therapeutic area since, as described above, we do not manage a significant portion of our R&D operations by development phase or by therapeutic area. Further, as we are able to adjust a significant portion of our spending quickly, as conditions change, we believe that any prior-period information about R&D expense by development phase or by therapeutic area would not necessarily be representative of future spending.

While a significant portion of R&D is done internally, we continue to seek out promising chemical and biological lead molecules and innovative technologies developed by third parties to incorporate into our discovery and development processes or projects, as well as our product lines, by entering into collaborations, alliances and license agreements with other companies, as well as leveraging acquisitions and equity- or debt-based investments. These agreements enable us to co-develop, license or acquire promising compounds, technologies or capabilities. We also enter into agreements pursuant to which a third party agrees to fund a portion of the development costs of one of our pipeline products in exchange for rights to receive potential milestone payments, revenue sharing payments, profit sharing payments and/or royalties. Collaboration, alliance, license and funding agreements and equity- or debt-based investments allow us to share risk and cost and to access external scientific and technological expertise, and enable us to advance our own products as well as in-licensed or acquired products.

For additional information about R&D by operating segment, see the "Analysis of Operating Segment Information" section of this MD&A. For additional information about our pending new drug applications and supplemental filings, see the "Analysis of the Condensed Consolidated Statements of Income—Product Developments—Biopharmaceutical" section of this MD&A. For additional information about recent transactions and strategic investments that we believe have the potential to advance our pipeline, see the "Our Strategy—Our Business Development Initiatives" section of this MD&A.

Intellectual Property Rights

We continue to aggressively defend our patent rights against increasingly aggressive infringement whenever appropriate, and we will continue to support efforts that strengthen worldwide recognition of patent rights while taking necessary steps to ensure appropriate patient access. In addition, we will continue to employ innovative approaches designed to prevent counterfeit pharmaceuticals from entering the supply chain and to achieve greater control over the distribution of our products, and we will continue to participate in the generics market for our products, whenever appropriate, once they lose exclusivity. Also, the pursuit of valid business opportunities may require us to challenge intellectual property rights held by other companies that we believe were improperly granted. Such challenges may include negotiation and litigation, which may not be successful. For additional information about our current efforts to enforce our intellectual property rights and certain other patent proceedings, see Notes to Condensed Consolidated Financial Statements — *Note 12A1. Contingencies and Certain Commitments : Legal Proceedings — Patent Litigation.* For information on risks related to patent protection and intellectual property claims by third parties, see "Risks Related to Intellectual Property" in Part I, Item 1A, "Risk Factors" of our 2017 Form 10-K.

Capital Allocation and Expense Management

We seek to maintain a strong balance sheet and robust liquidity so that we continue to have the financial resources necessary to take advantage of prudent commercial, research and business development opportunities and to directly enhance shareholder value through share repurchases and dividends. For additional information about our financial condition, liquidity, capital resources, share repurchases (including accelerated share repurchases) and dividends, see the "Analysis of Financial Condition, Liquidity and Capital Resources" section of this MD&A. For additional information about our recent business development activities, see the "Our Strategy—Our Business Development Initiatives" section of this MD&A.

We remain focused on achieving an appropriate cost structure for our company. For additional information about our cost-reduction and productivity initiatives, see the "Costs and Expenses—Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives" section of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 3 . Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* .

Increasing Investment in the U.S. —After evaluating the expected positive net impact the TCJA will have on us, we decided to take several actions:

- Over the next five years, we plan to invest approximately $5.0 billion in capital projects in the U.S., including the strengthening of our manufacturing presence in the U.S. As part of this plan, in July 2018, we announced that we will increase our commitment to U.S. manufacturing with a $465 million investment to build one of the most technically advanced sterile injectable pharmaceutical production facilities in the world in Portage, Michigan. This U.S. investment will strengthen our capability to produce and supply critical, life-saving injectable medicines for patients around the world.

Known as Modular Aseptic Processing, the new, multi-story, 400,000-square-foot production facility will also support the area economy by creating an estimated 450 new jobs over the next several years.

- We made a $500 million voluntary contribution to our U.S. pension plan in February 2018.
- In the fourth quarter of 2017, we made a $200 million charitable contribution to the Pfizer Foundation, an organization that provides grant and investment funding to support organizations and social entrepreneurs in an effort to improve healthcare delivery.
- In the first quarter of 2018, we paid a special, one-time bonus to virtually all Pfizer colleagues, excluding executives, of $119 million in the aggregate.

Our Business Development Initiatives

We are committed to capitalizing on growth opportunities by advancing our own pipeline and maximizing the value of our in-line products, as well as through various forms of business development, which can include alliances, licenses, joint ventures, collaborations, equity- or debt-based investments, dispositions, mergers and acquisitions. We view our business development activity as an enabler of our strategies, and we seek to generate earnings growth and enhance shareholder value by pursuing a disciplined, strategic and financial approach to evaluating business development opportunities. We continue to evaluate business development transactions that have the potential to strengthen our businesses and their capabilities, such as our acquisitions of Hospira, Medivation, Anacor, and AstraZeneca's small molecule anti-infectives business, as well as collaborations, and alliance and license agreements with other companies. We assess our businesses, assets and scientific capabilities/portfolio as part of our regular, ongoing portfolio review process and also continue to consider business development activities that will advance our businesses.

We continue to review strategic options for our Consumer Healthcare business. We remain disciplined regarding our capital allocation, and at this time we have not received an acceptable offer for the sale of this business. We will continue our management of this strong business as we explore other alternatives, which could include everything from a full or partial separation of the business to ultimately deciding to retain the business. We continue to expect that any decision regarding strategic alternatives for our Consumer Healthcare business will be made during the fourth quarter of 2018.

For additional information on our business development activities, see Notes to Condensed Consolidated Financial Statements— *Note 2. Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment* .

The more significant recent transactions and events are described below:

- Sale of Hospira Infusion Systems Net Assets to ICU Medical, Inc. (EH) —On February 3, 2017, we completed the sale of our global infusion systems net assets, HIS, to ICU Medical. In connection with this transaction, we recognized pre-tax income of $2 million in the third quarter of 2018 and pre-tax income of $1 million in the first nine months of 2018 , and we recognized pre-tax income of approximately $12 million in the third quarter of 2017 and a pre-tax loss of approximately $52 million in the first nine months of 2017 in *Other (income)/deductions—net* , representing adjustments to amounts previously recorded in 2016 to write down the HIS net assets to fair value less costs to sell. We may record additional adjustments to the loss on the sale of HIS net assets in future periods, which we do not expect to have a material impact on our consolidated financial statements.
- Acquisition of AstraZeneca's Small Molecule Anti-Infectives Business (EH) —On December 22, 2016, which fell in the first fiscal quarter of 2017 for our international operations, we acquired the development and commercialization rights to AstraZeneca's small molecule anti-infectives business, primarily outside the U.S. The total fair value of the consideration transferred for this business was approximately $555 million in cash plus the fair value of contingent consideration of $485 million .
- Research and Development Arrangement with NovaQuest Co-Investment Fund V, L.P. —In April 2016, Pfizer entered into an agreement with NovaQuest under which NovaQuest will fund up to $200 million in development costs related to certain Phase 3 clinical trials of Pfizer's rivipansel compound and Pfizer will use commercially reasonable efforts to develop and obtain regulatory approvals for such compound. NovaQuest's development funding is expected to cover up to 100% of the development costs and will be received over approximately 12 quarters from 2016 to 2019. As there is a substantive and genuine transfer of risk to NovaQuest, the development funding is recognized by us as an obligation to perform contractual services and therefore is a reduction of *Research and development expenses* as incurred. The reduction to *Research and development expenses* for the third quarter of 2018 totaled $12.9 million and for the first nine months of 2018 totaled $44.2 million . The reduction to *Research and development expenses* for the third quarter of 2017 totaled $16.8 million and for the first nine months of 2017 totaled $48.8 million . Following potential regulatory approval, NovaQuest will be eligible to receive a combination of fixed milestone payments of up to approximately $267 million in total, based on achievement of first commercial sale and certain levels of cumulative net sales as well as royalties on rivipansel net sales over approximately eight years. Fixed sales-based milestone payments will be recorded as intangible assets and amortized to *Amortization of*

intangible assets over the estimated commercial life of the rivipansel product and royalties on net sales will be recorded as *Cost of sales* when incurred.

- Research and Development Arrangement with RPI Finance Trust —In January 2016, Pfizer entered into an agreement with RPI, a subsidiary of Royalty Pharma, under which RPI will fund up to $300 million in development costs related to certain Phase 3 clinical trials of Pfizer's Ibrance (palbociclib) product primarily for adjuvant treatment of hormone receptor positive early breast cancer (the Indication). RPI's development funding is expected to cover up to 100% of the costs primarily for the applicable clinical trials through 2021. As there is a substantive and genuine transfer of risk to RPI, the development funding is recognized by us as an obligation to perform contractual services and therefore is a reduction of *Research and development expenses* as incurred. The reduction to *Research and development expenses* for the third quarter of 2018 totaled $27.1 million and for the first nine months of 2018 totaled $78.7 million . The reduction to *Research and development expenses* for the third quarter of 2017 totaled $27.6 million and for the first nine months of 2017 totaled $54.4 million . If successful and upon approval of Ibrance in the U.S. or certain major markets in the EU for the Indication based on the applicable clinical trials, RPI will be eligible to receive a combination of approval-based fixed milestone payments of up to $250 million dependent upon results of the clinical trials and royalties on certain Ibrance sales over approximately seven years. Fixed milestone payments due upon approval will be recorded as intangible assets and amortized to *Amortization of intangible assets* over the estimated commercial life of the Ibrance product and sales-based royalties will be recorded as *Cost of sales* when incurred.

For a description of the more significant recent transactions through February 22, 2018 , the filing date of our 2017 Form 10-K, see the "Our Business Development Initiatives" section of our 2017 Financial Report.

Our Financial Guidance for 2018

On October 30, 2018 , we updated our 2018 financial guidance to reflect our performance to date as well as our outlook for the remainder of the year. The midpoint of our guidance range for Adjusted diluted EPS was unchanged from our July 2018 guidance update.

The guidance range for Revenues was narrowed from a range of $53.0 to $55.0 billion to a range of $53.0 to $53.7 billion, primarily reflecting:

- lower-than-anticipated Essential Health revenues, primarily due to continued legacy Hospira Sterile Injectable Pharmaceuticals (SIP) product shortages in the U.S.; and
- recent unfavorable changes in foreign exchange rates in relation to the U.S. dollar from mid-July 2018 to mid-October 2018, primarily the weakening of certain emerging markets currencies and the euro.

Pfizer's updated 2018 financial guidance is presented below [(a), (b)] :

Revenues	$53.0 to $53.7 billion *(previously $53.0 to $55.0 billion)*
Adjusted cost of sales as a percentage of revenues	20.8% to 21.3% *(previously 20.5% to 21.5%)*
Adjusted selling, informational and administrative expenses	$14.0 to $14.5 billion *(previously $14.0 to $15.0 billion)*
Adjusted research and development expenses	$7.7 to $8.1 billion
Adjusted other (income)/deductions	Approximately $1.3 billion of income *(previously approximately $1.0 billion of income)*
Effective tax rate on adjusted income	Approximately 16.0%
Adjusted diluted EPS	$2.98 to $3.02 *(previously $2.95 to $3.05)*

[(a)] T he 2018 financial guidance reflects the following:

- A full year contribution from Consumer Healthcare. Pfizer continues to expect that any decision regarding strategic alternatives for Consumer Healthcare would be made during the fourth quarter of 2018.
- Does not assume the completion of any business development transactions not completed as of September 30, 2018 , including any one-time upfront payments associated with such transactions.
- Guidance for Adjusted other (income)/deductions does not attempt to forecast unrealized net gains or losses on equity securities. Pfizer is unable to predict with reasonable certainty unrealized gains or losses on equity securities in a given period. Net unrealized gains and losses on equity securities are now recorded in Adjusted other (income)/deductions during each quarter, reflecting the adoption of a new accounting standard in the first quarter of 2018 (see Notes to Condensed Consolidated Financial Statements— *Note 1B. Basis of Presentation and Significant Accounting Policies : Adoption of New Accounting Standards*). Prior to the adoption of the new standard, net unrealized gains and losses on virtually all equity securities with readily determinable fair values were reported in Accumulated other comprehensive income.
- Exchange rates assumed are a blend of the actual exchange rates in effect through third-quarter 2018 and mid-October 2018 exchange rates for the remainder of the year.

- Reflects an anticipated negative revenue impact of $1.8 billion due to recent and expected generic and biosimilar competition for certain products that have recently lost or are anticipated to soon lose patent protection. Assumes no generic competition for Lyrica in the U.S. until June 2019, which is contingent upon a six-month patent-term extension granted by the FDA for pediatric exclusivity, which the company is currently pursuing.
- Reflects the anticipated favorable impact of approximately $350 million on revenues and approximately $0.02 on adjusted diluted EPS as a result of favorable changes in foreign exchange rates relative to the U.S. dollar compared to foreign exchange rates from 2017 .
- Guidance for adjusted diluted EPS assumes diluted weighted-average shares outstanding of approximately 6.0 billion shares, which reflects anticipated share repurchases totaling approximately $12.0 billion in 2018, including $9.0 billion of share repurchases already completed through October 30, 2018. Dilution related to share-based employee compensation programs is expected to offset the reduction in shares associated with these share repurchases by approximately half.

(b) For an understanding of Adjusted income and its components and Adjusted diluted EPS (all of which are non-GAAP financial measures), see the "Non-GAAP Financial Measure (Adjusted Income)" section of this MD&A.

Pfizer does not provide guidance for GAAP Reported financial measures (other than revenues) or a reconciliation of forward-looking non-GAAP financial measures to the most directly comparable GAAP Reported financial measures on a forward-looking basis because it is unable to predict with reasonable certainty the ultimate outcome of pending litigation, unusual gains and losses, acquisition-related expenses and potential future asset impairments without unreasonable effort. These items are uncertain, depend on various factors, and could have a material impact on GAAP Reported results for the guidance period.

For information about our actual costs and anticipated costs and cost savings associated with our three-year cost-reduction initiative entered into in the fourth quarter of 2016 , the Hospira acquisition, our recent business development activities, and our current global commercial structure, see the "Costs and Expenses—Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives" section of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 3 . Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* .

Our 2018 financial guidance is subject to a number of factors and uncertainties as described in the "Our Operating Environment", "The Global Economic Environment", "Our Strategy" and "Forward-Looking Information and Factors That May Affect Future Results" sections of this MD&A; and Part I, Item 1A, "Risk Factors" of our 2017 Form 10-K and Part II, Item 1A, "Risk Factors" of this Quarterly Report on Form 10-Q.

SIGNIFICANT ACCOUNTING POLICIES AND APPLICATION OF CRITICAL ACCOUNTING ESTIMATES AND ASSUMPTIONS

For a description of our significant accounting policies, see Notes to Consolidated Financial Statements— *Note 1. Basis of Presentation and Significant Accounting Policies* in our 2017 Financial Report and Notes to Condensed Consolidated Financial Statements— *Note 1C. Basis of Presentation and Significant Accounting Policies* : *Revenues* . Of these policies, the following are considered critical to an understanding of our consolidated financial statements as they require the application of the most subjective and the most complex judgments: (i) Acquisitions (2017 Financial Report Note 1D); (ii) Fair Value (2017 Financial Report Note 1E); (iii) Revenues (Note 1C in this Quarterly Report on Form 10-Q); (iv) Asset Impairments (2017 Financial Report Note 1K); (v) Income Tax Assets and Liabilities and Income Tax Contingencies (2017 Financial Report Note 1O); (vi) Pension and Postretirement Benefit Plans (2017 Financial Report Note 1P); and Legal and Environmental Contingencies (2017 Financial Report Note 1Q).

For a discussion about the critical accounting estimates and assumptions impacting our consolidated financial statements, see the "Significant Accounting Policies and Application of Critical Accounting Estimates and Assumptions" section of our 2017 Financial Report. See also Notes to Consolidated Financial Statements— *Note 1C. Basis of Presentation and Significant Accounting Policies: Estimates and Assumptions* in our 2017 Financial Report for a discussion about the risks associated with estimates and assumptions.

For a discussion of recently adopted accounting standards and significant accounting policies, see Notes to Condensed Consolidated Financial Statements— *Note 1B. Basis of Presentation and Significant Accounting Policies : Adoption of New Accounting Standards* , *Note 1C. Basis of Presentation and Significant Accounting Policies : Revenues* and *Note 1D. Basis of Presentation and Significant Accounting Policies : Collaborative Arrangements* .

Revenues

Our gross product revenues are subject to a variety of deductions, which generally are estimated and recorded in the same period that the revenues are recognized. Such variable consideration represents chargebacks, rebates, sales allowances and sales returns. These deductions represent estimates of the related obligations and, as such, knowledge and judgment is required when estimating the impact of these revenue deductions on gross sales for a reporting period.

Historically, our adjustments of estimates, to reflect actual results or updated expectations, have not been material to our overall business. On a quarterly basis, our adjustments of estimates to reflect actual results generally have been less than 1% of revenues, and have resulted in either a net increase or a net decrease in revenues. Product-specific rebates, however, can have a significant impact on year-over-year individual product growth trends. If any of our ratios, factors, assessments, experiences or judgments are not indicative or accurate predictors of our future experience, our results could be materially affected. The sensitivity of our estimates can vary by program, type of customer and geographic location. However, estimates associated with U.S. Medicare, Medicaid and performance-based contract rebates are most at risk for material adjustment because of the extensive time delay between the recording of the accrual and its ultimate settlement, an interval that can generally range up to one year. Because of this time lag, in any given quarter, our adjustments to actual can incorporate revisions of several prior quarters.

Income Tax Assets and Liabilities

In the fourth quarter of 2017, we recorded an estimate of certain tax effects of the TCJA, including the impact on deferred tax assets and liabilities from the reduction in the U.S Federal corporate tax rate from 35% to 21% , the impact on valuation allowances and other state income tax considerations, a repatriation tax liability on accumulated post-1986 foreign earnings for which we plan to elect payment over eight years through 2026 that is reported primarily in *Other taxes payable* , and deferred taxes on basis differences expected to give rise to future taxes on global intangible low-taxed income. In addition, we had provided deferred tax liabilities in the past on foreign earnings that were not indefinitely reinvested. As a result of the TCJA, in the fourth quarter of 2017, we reversed an estimate of the deferred taxes that are no longer expected to be needed due to the change to the territorial tax system. The estimated amounts recorded may change in the future due to uncertain tax positions.

The TCJA subjects a U.S. shareholder to current tax on global intangible low-taxed income earned by certain foreign subsidiaries. The FASB Staff Q&A, Topic 740, No. 5, *Accounting for Global Intangible Low-Taxed Income* , states that we are permitted to make an accounting policy election to either recognize deferred taxes for temporary basis differences expected to reverse as global intangible low-taxed income in future years or provide for the tax expense related to such income in the year the tax is incurred. We have elected to recognize deferred taxes for temporary differences expected to reverse as global intangible low-taxed income in future years. However, given the complexity of these provisions, we have not finalized our analysis. We were able to make a reasonable estimate of the deferred taxes on the temporary differences expected to reverse in the future and provided a provisional deferred tax liability as of December 31, 2017. The provisional amount is based on the evaluation of certain temporary differences

inside each of our foreign subsidiaries that are expected to reverse as global intangible low-taxed income. However, as we continue to evaluate the TCJA's global intangible low-taxed income provisions during the measurement period, we may revise the methodology used for determining the deferred tax liability associated with such income.

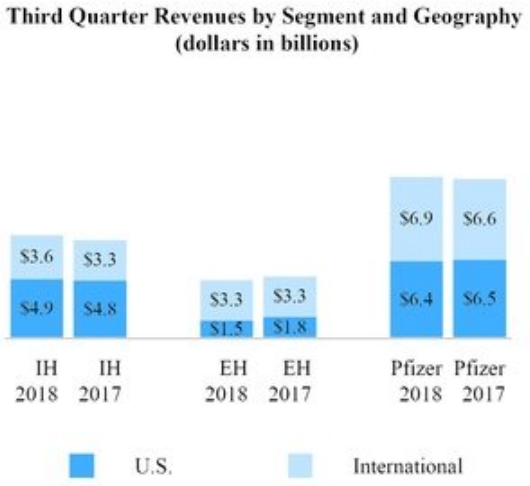
We believe that we have made reasonable estimates with respect to each of the above items, however, all of the amounts recorded remain provisional as we have not completed our analysis of the complex and far reaching effects of the TCJA. Further, we continue to consider our assertions on any remaining outside basis differences in our foreign subsidiaries as of September 30, 2018 and have not completed our analysis. In the third quarter of 2018, we recorded a favorable adjustment to the provisional estimate of the impact of the legislation, primarily related to the remeasurement of deferred tax assets and liabilities as well as revised estimates of benefits related to certain tax initiatives. Under guidance issued by the staff of the SEC, we expect to finalize our accounting related to the tax effects of the TCJA on deferred taxes, valuation allowances, state tax considerations, the repatriation tax liability, global intangible low-taxed income, and any remaining outside basis differences in our foreign subsidiaries during the fourth quarter of 2018, as we complete the remainder of our tax return filings and as any interpretations or clarifications of the TCJA occur through further legislation or U.S. Treasury actions or other means.

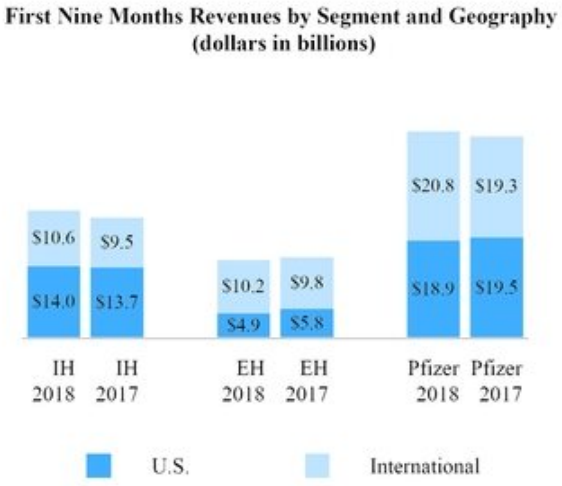
Income tax assets and liabilities also include income tax valuation allowances and accruals for uncertain tax positions. For additional information, see Notes to Consolidated Financial Statements— *Note 1C. Basis of Presentation and Significant Accounting Policies: Estimates and Assumptions* ; *Note 1O. Basis of Presentation and Significant Accounting Policies: Tax Assets and Liabilities and Income Tax Contingencies* and *Note 5A. Tax Matters: Taxes on Income from Continuing Operations* in our 2017 Form 10-K , as well as the "Analysis of Financial Condition, Liquidity and Capital Resources—Selected Measures of Liquidity and Capital Resources—Contractual Obligations" section of our 2017 Financial Report.

ANALYSIS OF THE CONDENSED CONSOLIDATED STATEMENTS OF INCOME

REVENUES AND PRODUCT DEVELOPMENTS

Revenues by Segment and Geography





The following tables provide worldwide revenues by operating segment and geography:

	Three Months Ended								
	Worldwide		U.S.		International		World-wide	U.S.	Inter-national
(MILLIONS OF DOLLARS)	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	% Change in Revenues		
Operating Segments [a]:									
IH	$ 8,471	$ 8,118	$ 4,881	$ 4,777	$ 3,590	$ 3,341	4	2	7
EH	4,826	5,050	1,480	1,756	3,347	3,294	(4)	(16)	2
Total revenues	$ 13,298	$ 13,168	$ 6,361	$ 6,534	$ 6,937	$ 6,634	1	(3)	5

	Nine Months Ended								
	Worldwide		U.S.		International		World-wide	U.S.	Inter-national
(MILLIONS OF DOLLARS)	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	Sep 30, 2018	Oct 1, 2017	% Change in Revenues		
Operating Segments [a]:									
IH	$ 24,573	$ 23,204	$ 14,002	$ 13,708	$ 10,572	$ 9,496	6	2	11
EH	15,097	15,639	4,859	5,808	10,238	9,831	(3)	(16)	4
Total revenues	$ 39,670	$ 38,843	$ 18,861	$ 19,516	$ 20,810	$ 19,327	2	(3)	8

[a] IH = the Innovative Health segment; and EH = the Essential Health segment. For additional information about each operating segment, see the "Our Strategy—Commercial Operations" and "Analysis of Operating Segment Information" sections of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 13A. Segment, Geographic and Other Revenue Information : Segment Information.*

Revenues— Third Quarter of 2018 vs. Third Quarter of 2017

The following provides an analysis of the worldwide change in revenues by geographic areas in the third quarter of 2018:

	Three Months Ended September 30, 2018		
(MILLIONS OF DOLLARS)	Worldwide	U.S.	International
Operational growth/(decline):			
Continued growth from certain key brands [a]	$ 660	$ 287	$ 373
Growth from Biosimilars, primarily from Inflectra in certain channels in the U.S., as well as in developed Europe	56	38	18
Growth from recently launched products, including Eucrisa in the U.S., as well as Besponsa and Bavencio, primarily in the U.S. and developed Europe	52	40	12
Lower revenues for total Viagra [b], primarily in the U.S. due to generic competition that began in December 2017	(169)	(165)	(4)
Decline from the Peri-LOE Products portfolio, driven by lower revenues in developed markets (excluding Viagra EH [b]), primarily due to expected declines in Lyrica in developed Europe	(125)	(61)	(64)
Decline in the LEP portfolio primarily driven by lower revenues in developed markets	(121)	(180)	59
Lower revenues for Enbrel, primarily in most developed Europe markets due to continued biosimilar competition	(65)	—	(65)
Decline from the SIP portfolio, driven by lower revenues in developed markets, primarily due to continued legacy Hospira product shortages in the U.S.	(28)	(58)	31
Other operational factors, net	(18)	(73)	55
Operational growth/(decline), net	243	(173)	415
Unfavorable impact of foreign exchange	(113)	—	(113)
Revenues increase/(decrease)	$ 130	$ (173)	$ 302

[a] Certain k ey brands represent Eliquis, Ibrance, Prevnar 13/Prevenar 13, Xeljanz and Xtandi. See the "Analysis of the Condensed Consolidated Statements of Income—Revenues—Selected Product Discussion" section of this MD&A for product analysis information.

[b] Viagra lost exclusivity in the U.S. in December 2017. Beginning in 2018, revenues for Viagra in the U.S. and Canada, which were reported in IH through 2017, are reported in EH (which reported all other Viagra revenues excluding the U.S. and Canada through 2017). Therefore, beginning in 2018, total Viagra revenues are reported in EH. Total Viagra revenues in 2017 represent the aggregate of worldwide revenues from Viagra IH and Viagra EH.

Emerging markets revenues increase d $226 million , or 8% , in the third quarter of 2018 to $3.1 billion from $2.8 billion , reflecting an operational increase of $356 million , or 13% . Foreign exchange had an unfavorable impact of approximately 5% on emerging markets revenues. The operational increase in emerging markets was driven by our EH segment, primarily by the Legacy Established Products portfolio and Sterile Injectable Pharmaceuticals portfolio, as well as Prevenar 13 in our IH segment.

Revenues—First Nine Months of 2018 vs. First Nine Months of 2017

The following provides an analysis of the change in worldwide revenues by geographic areas in the first nine months of 2018:

	Nine Months Ended September 30, 2018		
(MILLIONS OF DOLLARS)	Worldwide	U.S.	International
Operational growth/(decline):			
Continued growth from certain key brands [a]	$ 1,835	$ 822	$ 1,013
Growth from recently launched products, including Eucrisa in the U.S., as well as Besponsa and Bavencio, primarily in the U.S. and developed Europe	172	145	27
Growth from Biosimilars, primarily from Inflectra in certain channels in the U.S., as well as in developed Europe	165	115	50
Lower revenues for total Viagra [b], primarily in the U.S. due to generic competition that began in December 2017	(495)	(491)	(4)
Decline from the Peri-LOE Products portfolio, driven by lower revenues in developed markets (excluding Viagra EH [b]), primarily due to expected declines in Lyrica in developed Europe and Pristiq in the U.S. due to generic competition	(463)	(156)	(307)
Decline from the SIP portfolio, driven by lower revenues in developed markets, primarily due to continued legacy Hospira product shortages in the U.S.	(419)	(480)	61
Decline in the LEP portfolio, primarily driven by lower revenues in developed markets	(314)	(460)	145
Lower revenues for Enbrel, primarily in most developed Europe markets due to continued biosimilar competition	(279)	—	(279)
Impact on financial results for the sale of HIS in February 2017. The first nine months of 2018 do not reflect any contribution from HIS global operations, compared to approximately one month of HIS domestic operations and approximately two months of HIS international operations in the same period in 2017	(97)	(64)	(33)
Other operational factors, net	29	(88)	117
Operational growth/(decline), net	134	(655)	790
Favorable impact of foreign exchange	693	—	693
Revenues increase/(decrease)	$ 827	$ (655)	$ 1,483

[a] Certain k ey brands represent Eliquis, Ibrance, Xeljanz, Prevnar 13/Prevenar 13, Xtandi and Chantix/Champix. See the "Analysis of the Condensed Consolidated Statements of Income—Revenues—Selected Product Discussion" section of this MD&A for product analysis information .

[b] Viagra lost exclusivity in the U.S. in December 2017. Beginning in 2018, revenues for Viagra in the U.S. and Canada, which were reported in IH through 2017, are reported in EH (which reported all other Viagra revenues excluding the U.S. and Canada through 2017). Therefore, beginning in 2018, total Viagra revenues are reported in EH. Total Viagra revenues in 2017 represent the aggregate of worldwide revenues from Viagra IH and Viagra EH.

Emerging markets revenues increase d $1.1 billion , or 14% , in the first nine months of 2018 to $9.4 billion from $8.2 billion , reflecting an operational increase of $1.1 billion , or 13% . Foreign exchange had a favorable impact of approximately 1% on emerging markets revenues. The operational increase in emerging markets was driven by our EH segment, primarily by the Legacy Established Products portfolio and the Sterile Injectable Pharmaceuticals portfolio, as well as Prevenar 13 in our IH segment.

Revenue Deductions

Our gross product revenues are subject to a variety of deductions, which generally are estimated and recorded in the same period that the revenues are recognized. Such variable consideration represents chargebacks, rebates, sales allowances and sales returns. These deductions represent estimates of the related obligations and, as such, knowledge and judgment is required when estimating the impact of these revenue deductions on gross sales for a reporting period. Historically, our adjustments of estimates, to reflect actual results or updated expectations, have not been material to our overall business. On a quarterly basis, our adjustments of estimates to reflect actual results generally have been less than 1% of revenues, and have resulted in either a net increase or a net decrease in revenues. Product-specific rebates, however, can have a significant impact on year-over-year individual product growth trends. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 1C. Basis of Presentation and Significant Accounting Policies : Revenues.*

The following table provides information about revenue deductions:

(MILLIONS OF DOLLARS)	Three Months Ended		Nine Months Ended	
	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Medicare rebates [a]	$ 443	$ 355	$ 1,266	$ 931
Medicaid and related state program rebates [a]	502	439	1,500	1,335
Performance-based contract rebates [a], [b]	854	773	2,467	2,321
Chargebacks [c]	1,654	1,608	4,850	4,585
Sales allowances [d]	1,448	1,419	4,142	3,718
Sales returns and cash discounts	358	329	1,067	1,025
Total [e]	$ 5,259	$ 4,923	$ 15,292	$ 13,916

[a] Rebates are product-specific and, therefore, for any given year are impacted by the mix of products sold.

[b] Performance-based contract rebates include contract rebates with MCOs within the U.S., including health maintenance organizations and PBMs, who receive rebates based on the achievement of contracted performance terms and claims under these contracts. Outside the U.S., performance-based contract rebates include rebates to wholesalers/distributors based on achievement of contracted performance for specific products or sales milestones.

[c] Chargebacks primarily represent reimbursements to U.S. wholesalers for honoring contracted prices to third parties.

[d] Sales allowances primarily represent price reductions that are contractual or legislatively mandated outside the U.S., discounts and distribution fees.

[e] For the three months ended September 30, 2018 , associated with the following segments: IH ($2.3 billion) and EH ($2.9 billion). For the three months ended October 1, 2017 , associated with the following segments: IH ($2.4 billion); and EH ($2.5 billion). For the nine months ended September 30, 2018 , associated with the following segments: IH ($6.5 billion) and EH ($8.8 billion). For the nine months ended October 1, 2017 , associated with the following segments: IH ($6.4 billion) and EH ($7.5 billion).

Total revenue deductions for the third quarter of 2018 increase d 7% compared to the third quarter of 2017 , and total revenue deductions for the first nine months of 2018 increase d 10% compared to the first nine months of 2017 , primarily as a result of:

- an increase in sales allowances as a result of sales growth, primarily in international markets;
- an increase in Medicare rebates driven by increased sales of IH products through this channel;
- higher chargebacks to U.S. wholesalers on certain IH and EH products, partially offset by decreases in chargebacks as a result of decreases in sales of sterile injectable products; and
- an increase in Medicaid and related state program rebates, primarily as a result of increased sales of IH products through these programs.

For information on our accruals for Medicare rebates, Medicaid and related state program rebates, performance-based contract rebates, chargebacks, sales allowances and sales returns and cash discounts, including the balance sheet classification of these accruals, see Notes to Condensed Consolidated Financial Statements— *Note 1C. Basis of Presentation and Significant Accounting Policies : Revenues* .

Revenues—Selected Product Discussion

The tables below provide worldwide revenues, by geography, for selected products. References to total change pertain to period-over-period growth rates that include foreign exchange. The difference between the total change and operational change represents the impact of foreign exchange. Amounts may not add due to rounding. All percentages have been calculated using unrounded amounts. An asterisk (*) indicates the calculation is not meaningful or results are equal to or greater than 100%.

• **Prevnar 13/Prevenar 13** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 1,089	$ 971	12		$ 2,597	$ 2,554	2	
International	571	551	4	6	1,694	1,515	12	10
Worldwide revenues	$ 1,660	$ 1,522	9	10	$ 4,290	$ 4,069	5	5

The growth in the third quarter and first nine months of 2018 in the U.S. was primarily due to higher government purchases for the pediatric indication, partially offset by the continued decline in revenues for the adult indication due to a high initial capture rate of the eligible population following its successful fourth-quarter 2014 launch, which resulted in a smaller remaining "catch up" opportunity (i.e., the opportunity to reach adults aged 65 years and older who have not been previously vaccinated with Prevnar 13), compared to the prior-year period.

The operational growth in the third quarter of 2018 internationally was primarily due to higher volumes for the pediatric indication resulting from increased orders associated with Gavi, the Vaccine Alliance and from the second-quarter 2017 launch in China. The international operational growth in the first nine months of 2018 was primarily due to higher volumes for the pediatric indication resulting from the second-quarter 2017 launch in China and increased orders associated with Gavi, the Vaccine Alliance.

In 2014, the ACIP voted to recommend Prevnar 13 for routine use to help protect adults aged 65 years and older against pneumococcal disease, which for adults includes pneumonia caused by the 13 pneumococcal serotypes included in the vaccine. These ACIP recommendations were subsequently approved by the directors at the CDC and U.S. Department of Health and Human Services, and were published in the Morbidity and Mortality Weekly Report in September 2014 by the CDC. As with other vaccines, the CDC regularly monitors the impact of vaccination and reviews the recommendations. During the recently held October 2018 ACIP meeting, the CDC presented initial data and indicated formal evaluation of evidence (grading) and a potential vote on the maintenance of the 65 years and older recommendation would likely happen in 2019. A potential adverse change in the ACIP recommendation could negatively impact future Prevnar 13 revenues. We continue to generate and publish data and communicate with the ACIP on the burden of pneumococcal disease and Prevnar 13 vaccine effectiveness and safety.

We announced in September 2018 that our next generation 20-Valent Pneumococcal Vaccine candidate has received Breakthrough Therapy designation from the U.S. FDA.

• **Lyrica** (EH (revenues from all of Europe, Russia, Turkey, Israel and Central Asia)/IH (revenues from all other geographies)):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 875	$ 877	—		$ 2,643	$ 2,602	2	
International	338	408	(17)	(17)	1,006	1,208	(17)	(19)
Worldwide revenues	$ 1,213	$ 1,285	(6)	(5)	$ 3,649	$ 3,810	(4)	(5)

The relatively flat performance in the third quarter of 2018 in the U.S. was primarily due to sustained demand. The growth in the first nine months of 2018 in the U.S. was primarily driven by sustained demand and positive price impact.

The operational decline in the third quarter of 2018 internationally was primarily due to losses of exclusivity in developed Europe markets, Australia and South Korea. The operational decline in the first nine months of 2018 internationally was primarily due to losses of exclusivity in developed Europe markets, Australia and South Korea, partially offset by growth in the orally dissolving tablet formulation in Japan.

The following table provides worldwide revenues for Lyrica in our IH segment, by geography:

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 875	$ 877	—		$ 2,643	$ 2,602	2	
International	257	274	(6)	(6)	755	779	(3)	(5)
Worldwide revenues	$ 1,132	$ 1,150	(2)	(2)	$ 3,398	$ 3,382	—	—

Worldwide Lyrica revenues in our IH segment in the third quarter of 2018 decreased operationally, primarily due to losses of exclusivity in Australia in July 2017 and in South Korea in August 2017. The relatively flat performance in worldwide Lyrica revenues in our IH segment in the first nine months of 2018 was primarily due to losses of exclusivity in Australia and South Korea, offset by growth in the orally dissolving tablet formulation in Japan.

The following table provides worldwide revenues for Lyrica in our EH segment, by geography:

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ —	$ —	—		$ —	$ —	—	
International	81	134	(40)	(39)	251	428	(41)	(45)
Worldwide revenues	$ 81	$ 134	(40)	(39)	$ 251	$ 428	(41)	(45)

The worldwide operational decline s in our EH segment in the third quarter and first nine months of 2018 were primarily due to losses of exclusivity in developed Europe markets.

• **Ibrance** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 708	$ 713	(1)		$ 2,178	$ 2,048	6	
International	317	165	93	98	807	362	*	*
Worldwide revenues	$ 1,025	$ 878	17	18	$ 2,985	$ 2,410	24	23

The worldwide operational growth in the third quarter and first nine months of 2018 reflects an uptake in international markets, mostly driven by key European markets where we secured access and reimbursement in 2017 and the December 2017 launch in Japan as well as Ibrance class leadership among cyclin-dependent kinase inhibitors in major markets, supported by our scientific/clinical data and continued positive patient experience. The decline in the third quarter of 2018 in the U.S. was primarily due to the impact of competition and increased rebates. The growth in the first nine months of 2018 in the U.S. was primarily due to continued demand growth partially offset by uptake of competitors and increased rebates.

- **Eliquis alliance revenues and direct sales** (IH): Eliquis has been jointly developed and is commercialized by Pfizer and BMS. Pfizer funds between 50% and 60% of all development costs depending on the study. Profits and losses are shared equally on a global basis, except in certain countries where Pfizer commercializes Eliquis and pays BMS compensation based on a percentage of net sales. We have full commercialization rights in certain smaller markets. BMS supplies the product to us at cost plus a percentage of the net sales to end-customers in these markets. Eliquis is part of the Novel Oral Anticoagulant (NOAC) market; the agents in this class were developed as alternative treatment options to warfarin in appropriate patients.

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 455	$ 352	29		$ 1,371	$ 1,041	32	
International	416	291	43	44	1,153	772	49	42
Worldwide revenues	$ 870	$ 644	35	36	$ 2,524	$ 1,813	39	36

The worldwide operational growth in the third quarter and first nine months of 2018 was primarily driven by continued increased adoption in non-valvular atrial fibrillation, as well as oral anti-coagulant market share gain.

• **Lipitor** (EH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 25	$ 60	(58)		$ 86	$ 125	(32)	
International	482	431	12	11	1,453	1,215	20	14
Worldwide revenues	$ 507	$ 491	3	3	$ 1,539	$ 1,341	15	10

The worldwide operational growth in the third quarter of 2018 was primarily driven by increased demand in China, partially offset by the non-recurrence of favorable U.S. rebates that occurred in the third quarter of 2017 and pricing pressures in China. The worldwide operational growth in the first nine months of 2018 was primarily driven by increased demand in China and certain Middle Eastern markets, partially offset by pricing pressures in China, the non-recurrence of favorable U.S. rebates that occurred in the third quarter of 2017 and generic competition in Japan.

• **Enbrel** (IH, outside the U.S. and Canada):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ —	$ —	—		$ —	$ —	—	
International	531	613	(13)	(11)	1,589	1,818	(13)	(15)
Worldwide revenues	$ 531	$ 613	(13)	(11)	$ 1,589	$ 1,818	(13)	(15)

The worldwide operational decline s in the third quarter and first nine months of 2018 were primarily due to ongoing biosimilar competition in most developed Europe markets, which is expected to continue.

• **Xeljanz** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 332	$ 291	14		$ 964	$ 793	22	
International	100	57	76	84	256	142	81	81
Worldwide revenues	$ 432	$ 348	24	26	$ 1,221	$ 935	31	31

The growth in the U.S. in the third quarter and first nine months of 2018 was primarily driven by increased adoption among rheumatologists, growing awareness among patients and improvements in payer access, as well as launches of the psoriatic arthritis (PsA) indication in the first quarter of 2018 and ulcerative colitis indication in the third quarter of 2018.

The operational growth internationally in the third quarter and first nine months of 2018 was primarily driven by the 2017 approval of the rheumatoid arthritis indication in certain European markets, as well as continued uptake in Japan, Canada and emerging markets.

• **Sutent** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 80	$ 87	(7)		$ 262	$ 277	(6)	
International	168	189	(11)	(9)	524	527	(1)	(5)
Worldwide revenues	$ 248	$ 276	(10)	(9)	$ 785	$ 805	(2)	(5)

The worldwide operational decline s in the third quarter and first nine months of 2018 were primarily due to lower volumes driven by competitive pressure in the U.S. and certain developed and emerging Europe markets.

• **Norvasc** (EH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 9	$ 9	(2)		$ 27	$ 28	(4)	
International	238	217	10	10	745	656	14	9
Worldwide revenues	$ 247	$ 226	9	10	$ 773	$ 684	13	9

The worldwide operational growth in the third quarter and the first nine months of 2018 was primarily driven by increased demand in China, partially offset by generic competition in Japan and pricing pressures in China.

• **Chantix/Champix** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 197	$ 180	10		$ 602	$ 542	11	
International	64	60	6	7	187	184	2	(2)
Worldwide revenues	$ 261	$ 240	9	9	$ 789	$ 727	9	8

The growth in the U.S. in the third quarter and first nine months of 2018 was primarily due to increased volume, improved patient access and, for the first nine months of 2018 , positive price impact.

• The **Premarin** family of products (EH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 191	$ 224	(15)		$ 569	$ 670	(15)	
International	12	14	(14)	(12)	36	41	(13)	(14)
Worldwide revenues	$ 204	$ 238	(15)	(15)	$ 605	$ 711	(15)	(15)

The worldwide operational decline s in the third quarter and first nine months of 2018 were primarily driven by generic competition in the U.S.

• **Viagra** (EH): Viagra lost exclusivity in the U.S. in December 2017. Beginning in 2018, revenues for Viagra in the U.S. and Canada, which were reported in IH through 2017, are reported in EH (which reported all other Viagra revenues excluding the U.S. and Canada through 2017). Therefore, beginning in 2018, total Viagra revenues are reported in EH.

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 32	$ 198	(84)		$ 196	$ 687	(71)	
International	105	111	(5)	(3)	313	309	1	(1)
Worldwide revenues	$ 137	$ 308	(55)	(55)	$ 509	$ 996	(49)	(50)

The decline s in the U.S. in the third quarter and first nine months of 2018 were primarily due to the loss of exclusivity in December 2017.

The operational decline in the third quarter of 2018 internationally was primarily driven by lower volumes in Russia and Turkey and pricing pressures in China, partially offset by increased demand in China and Saudi Arabia.

• **Sulperazon** (EH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ —	$ —	—		$ —	$ —	—	
International	145	114	28	26	464	345	34	28
Worldwide revenues	$ 145	$ 114	28	26	$ 464	$ 345	34	28

The international operational growth in the third quarter and first nine months of 2018 was primarily due to increased demand in China.

• **Xtandi alliance revenues** (IH): Xtandi is being developed and commercialized through a collaboration with Astellas. The two companies share equally in the gross profits (losses) related to U.S. net sales of Xtandi. Subject to certain exceptions, Pfizer and Astellas also share equally all Xtandi commercialization costs attributable to the U.S. market. Pfizer and Astellas also share certain development and other collaboration expenses, and Pfizer receives tiered royalties as a percentage of international Xtandi net sales (recorded in *Other (income)/deductions—net*).

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 180	$ 150	20		$ 510	$ 422	21	
International	—	—	—	—	—	—	—	—
Worldwide revenues	$ 180	$ 150	20	20	$ 510	$ 422	21	21

The growth in the U.S. in the third quarter and first nine months of 2018 was primarily driven by continued growth of Xtandi in metastatic castration-resistant prostate cancer. While enrollment rates in patient assistance programs (PAP), which provide free medicines to patients, fluctuate throughout the year, we have observed a reduction in PAP utilization in the third quarter and first nine months of 2018, compared to the same periods in 2017.

• **Xalkori** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 34	$ 49	(31)		$ 118	$ 170	(31)	
International	93	96	(4)	(2)	299	272	10	5
Worldwide revenues	$ 127	$ 146	(13)	(12)	$ 417	$ 442	(6)	(9)

The worldwide operational decline s in the third quarter and first nine months of 2018 were primarily due to volume declines in the ALK indication across certain developed markets, primarily in the U.S. and certain markets in developed Europe, due to competitive pressure. The declines were partially offset by a continued increase in diagnostic rates for the ALK gene mutation across key markets and share in first-line ALK treatment outside the U.S., primarily in certain emerging markets, as well as uptake in treatment of patients with metastatic NSCLC whose tumors are ROS1-positive.

• **Celebrex** (EH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 16	$ 61	(73)		$ 50	$ 117	(57)	
International	171	150	14	14	444	448	(1)	(4)
Worldwide revenues	$ 188	$ 212	(11)	(11)	$ 494	$ 564	(12)	(15)

The worldwide operational decline in the third quarter of 2018 was primarily driven by the non-recurrence of the favorable U.S. rebates that occurred in the third quarter of 2017 and lower volumes in the U.S., as well as pricing pressure in Mexico, partially offset by increased demand in China and Japan. The worldwide operational decline in the first nine months of 2018 was primarily driven by the non-recurrence of the favorable U.S. rebates that occurred in the third quarter of 2017, lower volumes in the U.S., Japan and certain Middle Eastern markets, as well as pricing pressure in Mexico, partially offset by increased demand in China.

• **Inflectra/Remsima** (EH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 71	$ 34	*		$ 189	$ 74	*	
International	95	78	22	22	280	210	33	24
Worldwide revenues	$ 166	$ 112	48	48	$ 469	$ 284	65	58

The worldwide operational growth in the third quarter and first nine months of 2018 was due to continued uptake in certain channels in the U.S., as well as in developed markets in Europe, partially offset by pricing pressures in these markets.

Inflectra uptake in the U.S. is being driven by a number of factors including Inflectra's clinical data package, price and the access/reimbursement environment. To date, reimbursement coverage has been mixed. While we achieved 100% Medicare coverage, we have experienced access challenges among commercial payers where our lower priced product has not received access at parity to the innovator product and remains in a disadvantaged position despite the higher price of innovator product. We will look at all relevant factors impacting reimbursement given our extensive experience working with commercial payers to enable greater access for Inflectra. Additionally, in September 2017, Pfizer filed suit in the U.S. District Court for the Eastern District of Pennsylvania against J&J alleging that J&J's exclusionary contracts and other anticompetitive practices concerning Remicade ® (infliximab) violate federal antitrust laws.

• **Inlyta** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 27	$ 30	(10)		$ 88	$ 95	(7)	
International	44	53	(18)	(15)	138	161	(14)	(16)
Worldwide revenues	$ 71	$ 84	(15)	(13)	$ 226	$ 256	(12)	(13)

The worldwide operational decline in the third quarter of 2018 was primarily due to increased competition across developed markets. The worldwide operational decline in the first nine months of 2018 was primarily due to increased competition across developed markets, as well as China.

• **Eucrisa** (IH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 40	$ 15	*		$ 104	$ 33	*	
International	—	—	—	—	—	—	—	—
Worldwide revenues	$ 40	$ 15	*	*	$ 104	$ 33	*	*

The worldwide operational growth in the third quarter and first nine months of 2018 was primarily driven by broader prescriber trial and adoption, as well as growing patient awareness and interest.

• **Alliance revenues** (IH/EH):

	Three Months Ended				Nine Months Ended			
			% Change				% Change	
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	Total	Oper.	September 30, 2018	October 1, 2017	Total	Oper.
U.S.	$ 642	$ 507	26		$ 1,901	$ 1,487	28	
International	336	234	44	43	919	624	47	39
Worldwide revenues	$ 977	$ 741	32	32	$ 2,820	$ 2,112	34	31

The worldwide operational growth in the third quarter and first nine months of 2018 was mainly due to increases in Eliquis and Xtandi alliance revenues discussed above.

◦ **Bavencio** (IH) is being developed and commercialized in collaboration with Merck KGaA. Both companies jointly fund all development and commercialization costs, and split equally any profits generated from selling any anti-PD-L1 or anti-PD-1 products from this collaboration. Bavencio is currently approved in metastatic MCC in the U.S., Europe, Japan, and selected other markets, as well as in second line treatment of locally advanced or metastatic urothelial carcinoma in the U.S.

See Notes to Condensed Consolidated Financial Statements— *Note 13C. Segment, Geographic and Other Revenue Information* : *Other Revenue Information* for additional information regarding the primary indications or class of the selected products discussed above.

See Notes to Condensed Consolidated Financial Statements— *Note 12. Contingencies and Certain Commitments* for a discussion of recent developments concerning patent and product litigation relating to certain of the products discussed above.

Product Developments—Biopharmaceutical

We continue to invest in R&D to provide potential future sources of revenues through the development of new products, as well as through additional uses for in-line and alliance products. Notwithstanding our efforts, there are no assurances as to when, or if, we will receive regulatory approval for additional indications for existing products or any of our other products in development.

We continue to strengthen our global R&D organization and pursue strategies intended to improve innovation and overall productivity in R&D to achieve a sustainable pipeline that will deliver value in the near term and over time.

For additional information about our R&D organization, see the "Overview of Our Performance, Operating Environment, Strategy and Outlook—Our Strategy—Organizing for Growth" and "—Description of Research and Development Operations" sections of this MD&A.

A comprehensive update of Pfizer's development pipeline was published as of October 30, 2018 and is available at www.pfizer.com/science/drug-product-pipeline. It includes an overview of our research and a list of compounds in development with targeted indication and phase of development, as well as mechanism of action for some candidates in Phase 1 and all candidates from Phase 2 through registration.

The following series of tables provides information about significant regulatory actions by, and filings pending with, the FDA and regulatory authorities in the EU and Japan, as well as additional indications and new drug candidates in late-stage development.

RECENT FDA APPROVALS		
PRODUCT	**INDICATION**	**DATE APPROVED**
Lorbrena (lorlatinib)	Treatment of patients with ALK-positive metastatic NSCLC whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease	November 2018
Talzenna (talazoparib)	Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (*gBRCAm*) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer	October 2018
Vizimpro (dacomitinib)	First-line treatment of patients with metastatic non-small cell lung cancer with epidermal growth factor receptor exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test, which is being developed in collaboration with SFJ	September 2018
Nivestym (filgrastim-aafi) [(a)]	A biosimilar to Neupogen® (filgrastim) for all eligible indications of the reference product	July 2018
Xtandi (enzalutamide)	Treatment of men with non-metastatic castration-resistant prostate cancer, which is being developed through a collaboration with Astellas	July 2018
Xeljanz (tofacitinib)	Treatment of adult patients with moderately to severely active ulcerative colitis	May 2018
Retacrit (epoetin alfa-epbx) [(b)]	A biosimilar to Epogen® and Procrit® (epoetin alfa) for all indications of the reference product	May 2018
Steglatro (ertugliflozin)	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, which is being developed in collaboration with Merck	December 2017
Segluromet (ertugliflozin and metformin)	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin, which is being developed in collaboration with Merck	December 2017
Steglujan (ertugliflozin and sitagliptin)	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate, which is being developed in collaboration with Merck	December 2017
Bosulif (bosutinib)	Treatment of adult patients with newly-diagnosed chronic phase Philadelphia chromosome-positive Ph+ CML, which is being developed in collaboration with Avillion	December 2017
Xeljanz (tofacitinib) and Xeljanz XR	Xeljanz 5 mg twice daily and Xeljanz XR extended release 11 mg once daily for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs	December 2017
Sutent (sunitinib)	Adjuvant treatment in adult patients at high risk of recurrent renal cell carcinoma following nephrectomy (surgical removal of the cancerous kidney)	November 2017

[(a)] Neupogen® is a registered trademark of Amgen Inc.
[(b)] Epogen® is a registered U.S. trademark of Amgen Inc.; Procrit® is a registered U.S. trademark of J&J.

PENDING U.S. NDAs AND SUPPLEMENTAL FILINGS		
PRODUCT	**PROPOSED INDICATION**	**DATE FILED***
PF-05280586 [(a)]	A potential biosimilar to Rituxan® (rituximab)	September 2018
PF-06439535 [(b)]	A potential biosimilar to Avastin® (bevacizumab)	August 2018
glasdegib	Treatment of adult patients with previously untreated acute myeloid leukemia in combination with low-dose cytarabine, a type of chemotherapy	June 2018
PF-05280014 [(c)]	A potential biosimilar to Herceptin® (trastuzumab)	August 2017
tafamidis meglumine [(d)]	Treatment of transthyretin familial amyloid polyneuropathy	February 2012

* The dates set forth in this column are the dates on which the FDA accepted our submissions.
[(a)] Rituxan ® is a registered trademark of Biogen MA Inc.
[(b)] Avastin ® is a registered trademark of Genentech, Inc.
[(c)] Herceptin ® is a registered trademark of Genentech, Inc. In April 2018, we received a "complete response" letter from the FDA with respect to our biologics license application (BLA) for PF-05280014, our proposed biosimilar to trastuzumab, which was submitted for all indications of the reference product. The FDA highlighted the need for additional technical information, which does not relate to safety or clinical data submitted in the application. In October 2018, the FDA acknowledged for review our BLA resubmission.

(d) In May 2012, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted that the tafamidis meglumine data provide substantial evidence of efficacy for a surrogate endpoint that is reasonably likely to predict a clinical benefit. In June 2012, the FDA issued a "complete response" letter with respect to the tafamidis NDA. The FDA has requested the completion of a second efficacy study, and also has asked for additional information on the data within the current tafamidis NDA. Pfizer has completed study B3461028, a global Phase 3 study to support a potential new indication in transthyretin cardiomyopathy, which includes patients with wild type and variant transthyretin. This study has achieved its primary endpoint, and we are working with the FDA to identify next steps.

REGULATORY APPROVALS AND FILINGS IN THE EU AND JAPAN			
PRODUCT	**DESCRIPTION OF EVENT**	**DATE APPROVED**	**DATE FILED***
Vyndaqel (tafamidis meglumine)	Application filed in Japan for treatment of transthyretin amyloid cardiomyopathy (ATTR-CM)	—	November 2018
Xtandi (enzalutamide)	Application approved in the EU for treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer, which is being developed through a collaboration with Astellas	October 2018	—
Trastuzumab BS for I.V. Infusion 60mg/150mg "Pfizer" (a)	Application approved in Japan for a biosimilar to Herceptin® (trastuzumab)	September 2018	—
Lorbrena (lorlatinib)	Application approved in Japan for the treatment of patients with ALK-positive metastatic non-small cell lung cancer, previously treated with one or more ALK inhibitor	September 2018	—
PF-05280586 (b)	Application filed in the EU for a potential biosimilar to Rituxan® (rituximab)	—	August 2018
Xeljanz (tofacitinib)	Application approved in the EU for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent	July 2018	—
Trazimera (a)	Application approved in the EU for a biosimilar to Herceptin® (trastuzumab) for the treatment of human epidermal growth factor (HER2) overexpressing breast cancer and HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	July 2018	—
Infliximab BS for I.V. Infusion 100mg "Pfizer" (c)	Application approved in Japan for a biosimilar to Remicade® (infliximab)	July 2018	—
Xeljanz (tofacitinib)	Application approved in the EU for Xeljanz in combination with methotrexate for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug therapy	June 2018	—
talazoparib	Application filed in the EU for the treatment of patients with germline BRCA-mutated advanced breast cancer	—	June 2018
Xeljanz (tofacitinib)	Application approved in Japan for the treatment of ulcerative colitis	May 2018	—
dacomitinib	Application filed in Japan for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) mutations, which is being developed in collaboration with SFJ	—	May 2018
crisaborole	Application filed in the EU for the treatment of mild-to-moderate atopic dermatitis	—	May 2018
Mylotarg (gemtuzumab ozogamicin)	Application approved in the EU for treatment of patients age 15 years and above with previously untreated, de novo, CD33-positive acute myeloid leukemia, except acute promyelocytic leukemia	April 2018	—
Bosulif (bosutinib)	Application approved in the EU for the treatment of adults with newly diagnosed chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML), which is being developed in collaboration with Avillion	April 2018	—
dacomitinib	Application filed in the EU for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations, which is being developed in collaboration with SFJ	—	March 2018
Steglatro (ertugliflozin)	Approval in the EU as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: • as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; and • in addition to other medicinal products for the treatment of diabetes, which is being developed in collaboration with Merck	March 2018	—
Segluromet (ertugliflozin and metformin)	Approval in the EU as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: • in patients not adequately controlled on their maximally tolerated dose of metformin alone; • in patients on their maximally tolerated doses of metformin in addition to other medicinal products for the treatment of diabetes; and • in patients already being treated with the combination of ertugliflozin and metformin as separate tablets, which is being developed in collaboration with Merck	March 2018	—
Steglujan (ertugliflozin and sitagliptin)	Approval in the EU as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: • when metformin and/or a sulphonylurea (SU) and one of the monocomponents of Steglujan do not provide adequate glycaemic control; and • in patients already being treated with the combination of ertugliflozin and sitagliptin as separate tablets, which is being developed in collaboration with Merck	March 2018	—
PF-06439535 (d)	Application filed in the EU for a potential biosimilar to Avastin® (bevacizumab)	—	March 2018
Xeljanz (tofacitinib)	Application filed in the EU for modified release 11mg tablet for rheumatoid arthritis	—	March 2018
lorlatinib (PF-06463922)	Application filed in the EU for the treatment of patients with ALK-positive metastatic non-small cell lung cancer, previously treated with one or more ALK inhibitors	—	February 2018
Besponsa (inotuzumab ozogamicin)	Approval in Japan for the treatment of relapsed or refractory CD 22- positive acute lymphoblastic leukemia	January 2018	—

* For applications in the EU, the dates set forth in this column are the dates on which the EMA validated our submissions.

(a) Herceptin ® is a registered trademark of Genentech, Inc.

(b) Rituxan ® is a registered trademark of Biogen MA Inc.

(c) Remicade ® is a registered Japan trademark of Janssen. In February 2016, we divested the rights for development and commercialization of PF-06438179, a potential biosimilar to Remicade ® (infliximab) in the 28 countries that form the EEA to Sandoz, which was a condition to the European Commission's approval of the Hospira transaction. We retain commercialization rights to PF-06438179 in all countries outside of the EEA.
(d) Avastin® is a registered trademark of Genentech, Inc.

LATE-STAGE CLINICAL PROGRAMS FOR ADDITIONAL USES AND DOSAGE FORMS FOR IN-LINE AND IN-REGISTRATION PRODUCTS	
PRODUCT	**PROPOSED INDICATION**
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1, in combination with Inlyta (axitinib), a tyrosine kinase inhibitor, for the first-line treatment of advanced renal cell carcinoma, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1, in combination with talazoparib in patients with previously untreated advanced ovarian cancer, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1 for the first-line treatment of stage IIIb/IV non-small cell lung cancer, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab) (a)	A monoclonal antibody that inhibits PD-L1 for treatment of stage IIIb/IV non-small cell lung cancer that has progressed after a platinum-containing doublet, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1 for treatment of platinum-resistant/refractory ovarian cancer, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1 for the first-line treatment of ovarian cancer, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1 for maintenance treatment, in the first-line setting, for patients with urothelial cancer, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1 for maintenance treatment of advanced or metastatic gastric/ gastro-esophageal junction cancers, which is being developed in collaboration with Merck KGaA, Germany
Bavencio (avelumab)	A monoclonal antibody that inhibits PD-L1 for treatment of locally advanced squamous cell carcinoma of the head and neck, which is being developed in collaboration with Merck KGaA, Germany
Ibrance (palbociclib)	Treatment of HER2+ advanced breast cancer, in collaboration with the Alliance Foundation Trials, LLC
Ibrance (palbociclib)	Treatment of high-risk early breast cancer, in collaboration with the German Breast Group
Ibrance (palbociclib)	Treatment of HR+ early breast cancer, in collaboration with the Alliance Foundation Trials, LLC, and the Austrian Breast Colorectal Cancer Study Group
Xeljanz (tofacitinib)	Treatment of ankylosing spondylitis
Xtandi (enzalutamide)	Treatment of non-metastatic high risk hormone-sensitive prostate cancer, which is being developed through a collaboration with Astellas
Xtandi (enzalutamide)	Treatment of metastatic hormone-sensitive prostate cancer, which is being developed through a collaboration with Astellas
Vyndaqel (tafamidis meglumine)	Adult symptomatic transthyretin cardiomyopathy (ex-Japan)

(a) In February 2018, we and our partner Merck KGaA, Darmstadt, Germany, announced that the Bavencio Phase 3 trial in second-line NSCLC did not meet its pre-specified primary endpoint. We are continuing to further evaluate the detailed results.

NEW DRUG CANDIDATES IN LATE-STAGE DEVELOPMENT	
CANDIDATE	**PROPOSED INDICATION**
glasdegib (PF-0444913)	A smoothened inhibitor for the treatment of acute myeloid leukemia
lorlatinib (PF-06463922)	A next generation ALK/ROS1 tyrosine kinase inhibitor for the first-line treatment of patients with ALK-positive advanced non-small cell lung cancer
fidanacogene elaparvovec (PF-06838435)	An investigational gene therapy for the treatment of hemophilia B
PF-04965842	A Janus kinase 1 (JAK1) inhibitor for the treatment of moderate-to-severe atopic dermatitis
PF-06425090	A prophylactic vaccine for active immunization to prevent clostridium difficile colitis
PF-06410293 (a)	A potential biosimilar to Humira® (adalimumab)
rivipansel (GMI-1070)	A pan-selectin inhibitor for the treatment of vaso-occlusive crisis in hospitalized individuals with sickle cell disease, which was licensed from GlycoMimetics Inc.
somatrogon (PF-06836922)	A long-acting hGH-CTP for the treatment of growth hormone deficiency in children, which is being developed in collaboration with OPKO
somatrogon (PF-06836922)	A long-acting hGH-CTP for the treatment of growth hormone deficiency in adults, which is being developed in collaboration with OPKO
talazoparib (MDV3800)	An oral PARP inhibitor for the treatment of metastatic castration-resistant prostate cancer
tanezumab	An anti-nerve growth factor monoclonal antibody for the treatment of pain, which is being developed in collaboration with Lilly

(a) Humira ® is a registered trademark of AbbVie Biotechnology Ltd.

Additional product-related programs are in various stages of discovery and development. Also, see the discussion in the "Our Strategy—Our Business Development Initiatives" section of this MD&A.

COSTS AND EXPENSES

The changes in expenses below reflect, among other things, the favorable impact of the February 2017 sale of HIS. The operating results of HIS are included in our operating results through February 2, 2017 and, therefore, operating results for the third quarter of 2017 do not reflect any contribution from HIS global operations, while the first nine months of 2017 reflect approximately one month of HIS domestic operations and approximately two months of HIS international operations. Our operating results for 2018 do not reflect any HIS global operations.

Cost of Sales

	Three Months Ended			Nine Months Ended		
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
Cost of sales	$ 2,694	$ 2,844	(5)	$ 8,173	$ 7,972	3
As a percentage of *Revenues*	20.3%	21.6%		20.6%	20.5%	

Cost of sales decrease d 5% in the third quarter of 2018 , compared to the same period in 2017 , primarily due to:

- the favorable impact of foreign exchange of $212 million and the favorable impact of hedging activity on intercompany inventory of $18 million ;
- lower volumes driven by the SIP portfolio, primarily due to legacy Hospira product shortages in the U.S., as well as generic competition in developed markets; and
- the non-recurrence of $55 million in inventory losses, overhead costs, and incremental costs related to the period in 2017 during which our Puerto Rico plants were not operational due to hurricanes,

partially offset by:

- increased sales volumes for various key products within our product portfolio;
- higher costs across the SIP portfolio, as a result of the complexity of high quality product manufacture across the legacy Hospira plants; and
- an increase in royalty expenses based on the mix of products sold.

Cost of sales increased 3% in the first nine months of 2018 , compared to the same period in 2017 , primarily due to:

- the unfavorable impact of foreign exchange of $157 million and the unfavorable impact of hedging activity on intercompany inventory of $114 million ;
- increased sales volumes for various key products within our product portfolio; and
- an increase in royalty expenses based on the mix of products sold,

partially offset by:

- lower volumes driven by the SIP portfolio, primarily due to legacy Hospira product shortages in the U.S., as well as generic competition in developed markets;
- the non-recurrence of $55 million in inventory losses, overhead costs, and incremental costs related to the period in 2017 during which our Puerto Rico plants were not operational due to hurricanes; and
- the non-recurrence of charges related to a product recall that occurred in 2017.

The decrease in *Cost of sales* as a percentage of revenues in the third quarter of 2018 and the slight increase in *Cost of sales* as a percentage of revenues for the first nine months of 2018 , compared to the same periods in 2017 , was primarily due to all of the factors discussed above, as well as an increase in alliance revenues, which have no associated cost of sales.

Selling, Informational and Administrative (SI&A) Expenses

	Three Months Ended			Nine Months Ended		
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
Selling, informational and administrative expenses	$ 3,494	$ 3,504	—	$ 10,448	$ 10,249	2
As a percentage of *Revenues*	26.3%	26.6%		26.3%	26.4%	

SI&A expenses remained relatively flat in the third quarter of 2018 , compared to the same period in 2017 , primarily due to:

- lower advertising, promotional and field force expenses, reflecting the benefits of cost-reduction and productivity initiatives;
- lower general and administrative expenses;
- lower healthcare reform expenses as a result of a true up of the prior year amount; and

- the favorable impact of foreign exchange of $24 million ,

largely offset by:

- additional investment across several of our key products, primarily Xeljanz, Eucrisa, Eliquis and Prevnar 13/Prevenar 13 (pediatric indication); and
- additional investments in China.

SI&A expenses increased 2% in the first nine months of 2018 , compared to the same period in 2017 , primarily due to:

- additional investment across several of our key products, primarily Xeljanz, Eucrisa, Ibrance, Prevnar 13/Prevenar 13 (pediatric indication) and Eliquis;
- the unfavorable impact of foreign exchange of $152 million ;
- a special, one-time bonus paid to virtually all Pfizer colleagues, excluding executives, of $119 million , in the aggregate, in the first quarter of 2018; and
- additional investments in China,

partially offset by:

- lower advertising, promotional and field force expenses, reflecting the benefits of cost-reduction and productivity initiatives;
- lower general and administrative expenses;
- lower healthcare reform expenses as a result of a true up of the prior year amount; and
- decreased investment in Enbrel due to loss of exclusivity across developed Europe.

Research and Development (R&D) Expenses

	Three Months Ended			Nine Months Ended		
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
Research and development expenses	$ 2,008	$ 1,865	8	$ 5,549	$ 5,367	3
As a percentage of *Revenues*	15.1%	14.2%		14.0%	13.8%	

R&D expenses increase d 8% in the third quarter and 3% the first nine months of 2018 , compared to the same periods in 2017 , due to:

- increased costs associated with:
  - our Oncology portfolio, including costs associated with Bavencio studies;
  - our Phase 3 clinical trial related to our JAK1 inhibitor (which was initiated in December 2017), as well as, in the first nine months of 2018 , our Phase 3 clinical trial related to the *C. difficile* vaccine program (which was initiated in March 2017);
- an increase in the value of the portfolio performance share grants reflecting changes in the price of Pfizer's common stock, as well as management's assessment of the probability that the specified performance criteria will be achieved;
- the timing of milestone activity; and
- increased spend on our rare disease portfolio,

partially offset by:

- decreased spending for biosimilars as several programs have reached completion;
- lower costs due to the completion of certain tanezumab studies;
- the phase out of the Lyrica clinical studies; and
- the impact of our decision to end internal neuroscience discovery and early development efforts.

For additional information on Cost of sales, SI&A and R&D expenses by operating segment, see the "Analysis of Operating Segment Information" section of this MD&A.

Amortization of Intangible Assets

	Three Months Ended			Nine Months Ended		
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
Amortization of intangible assets	$ 1,253	$ 1,177	6	$ 3,640	$ 3,571	2
As a percentage of *Revenues*	9.4%	8.9%		9.2%	9.2%	

See also Notes to Condensed Consolidated Financial Statements— *Note 9A. Identifiable Intangible Assets and Goodwill: Identifiable Intangible Assets.*

Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives

(MILLIONS OF DOLLARS)	Three Months Ended			Nine Months Ended		
	Sep 30, 2018	Oct 1, 2017	% Change	Sep 30, 2018	Oct 1, 2017	% Change
Restructuring charges—acquisition-related costs [a]	$ 24	$ 70	(66)	$ 5	$ 80	(94)
Restructuring credits—cost reduction initiatives [b]	(22)	(15)	54	(37)	(52)	(29)
Restructuring charges/(credits)	1	56	(98)	(32)	28	*
Transaction costs [c]	1	(14)	*	1	4	(59)
Integration costs [c]	82	73	13	202	235	(14)
Restructuring charges and certain acquisition-related costs	85	114	(26)	172	267	(36)
Net periodic benefit costs [d]	41	35	16	103	110	(7)
Additional depreciation—asset restructuring	12	39	(69)	43	74	(42)
Total implementation costs	48	57	(16)	130	150	(13)
Costs associated with acquisitions and cost-reduction/productivity initiatives [e]	$ 186	$ 245	(24)	$ 447	$ 601	(26)

* Calculation not meaningful or results are equal to or greater than 100%.

[a] Restructuring charges—acquisition-related costs include employee termination costs, asset impairments and other exit costs associated with business combinations. Charges for the third quarter of 2018 were primarily due to accruals for exit costs and asset write downs related to our acquisition of Hospira, and charges for the first nine months of 2018 were primarily due to asset write downs related to our acquisition of Hospira, partially offset by the reversal of previously recorded accruals for employee termination costs related to our acquisition of Hospira. Restructuring charges for the third quarter and first nine months of 2017 were mainly related to our acquisitions of Hospira and Medivation.

[b] Restructuring credits—cost reduction initiatives relate to employee termination costs, asset impairments and other exit costs not associated with acquisitions. For the third quarter and first nine months of 2018 and 2017 , the credits are mostly related to the reversal of previously recorded accruals for employee termination costs.

[c] For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* .

[d] For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 1B . Basis of Presentation and Significant Accounting Policies : Adoption of New Accounting Standards* and *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* .

[e] Comprises *Restructuring charges and certain acquisition-related costs* as well as costs associated with our cost-reduction/productivity initiatives included in *Cost of sales* , *Research and development expenses, Selling, informational and administrative expenses* and/or *Other (income)/deductions—net* as appropriate. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* .

In connection with our acquisition of Hospira in September 2015, we focused our efforts on achieving an appropriate cost structure for the combined company. We achieved our $1 billion of annual cost savings in connection with the Hospira acquisition, 25% more than our initial cost savings target of $800 million. The one-time costs to generate the savings are expected to be approximately $1 billion (not including costs of $215 million associated with the return of acquired IPR&D rights), and the majority of these costs were incurred within the three-year period post-acquisition.

New Cost-Reduction/Productivity Initiatives — 2017 through 2019 Activities

As a result of the evaluation performed in connection with our decision in September 2016 to not pursue, at that time, splitting IH and EH into two separate publicly-traded companies, we identified new opportunities to potentially achieve greater optimization and efficiency to become more competitive in our business. Therefore, in early 2017, we initiated new enterprise-wide cost-reduction/productivity initiatives, which we expect to substantially complete by the end of 2019. These initiatives encompass all areas of our cost base and include further centralization of our corporate and platform functions and optimization of our manufacturing plant network to support IH and EH products and pipelines, as well as activities in other areas where opportunities are identified. The action plans related to these new initiatives are underway and, in order to achieve targeted savings of approximately $1.4 billion by 2020, we expect to incur total costs of approximately $1.2 billion over the three-year period, 2017-2019. Of this amount, we expect about 60% to be manufacturing operations related and we expect about 20% of the total charges will be non-cash. For additional information about these programs and expected and actual total costs, see Notes to Condensed Consolidated Financial Statements— *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* . The expected cost savings in 2018 associated with these activities are reflected in our 2018 financial guidance.

In addition to these major initiatives, we continuously monitor our operations for cost reduction and/or productivity opportunities, especially in light of the losses of exclusivity and the expiration of collaborative arrangements for various products.

Other (Income)/Deductions—Net

	Three Months Ended			Nine Months Ended		
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
Other (income)/deductions—net	$ (414)	$ 79	*	$ (1,143)	$ 65	*

* Calculation not meaningful or results are equal to or greater than 100%.

For information about the components of *Other (income)/deductions—net* , see Notes to Condensed Consolidated Financial Statements— *Note 4. Other (Income)/Deductions—Net* .

See also the "Analysis of Operating Segment Information" section of this MD&A.

PROVISION FOR TAXES ON INCOME

	Three Months Ended			Nine Months Ended		
(MILLIONS OF DOLLARS)	September 30, 2018	October 1, 2017	% Change	September 30, 2018	October 1, 2017	% Change
Provision for taxes on income	$ 66	$ 727	(91)	$ 1,270	$ 2,287	(44)
Effective tax rate on continuing operations	1.6%	20.3%		9.9%	20.1%	

For information about our effective tax rate and the events and circumstances contributing to the changes between periods, see Notes to Condensed Consolidated Financial Statements— *Note 5. Tax Matters* .

NON-GAAP FINANCIAL MEASURE (ADJUSTED INCOME)

General Description of Non-GAAP Financial Measure (Adjusted Income)

Adjusted income is an alternative view of performance used by management. We measure the performance of the overall Company on this basis in conjunction with other performance metrics. Because Adjusted income is an important internal measurement for Pfizer, we believe that investors' understanding of our performance is enhanced by disclosing this performance measure. We report Adjusted income, certain components of Adjusted income, and Adjusted diluted earnings per share in order to portray the results of our major operations—the discovery, development, manufacture, marketing and sale of prescription medicines, vaccines and consumer healthcare (OTC) products—prior to considering certain income statement elements. We have defined Adjusted income as *Net income attributable to Pfizer Inc.* before the impact of purchase accounting for acquisitions, acquisition-related costs, discontinued operations and certain significant items, which are described below. Also, see the "Non-GAAP Financial Measure (Adjusted Income)—General Description of Non-GAAP Financial Measure (Adjusted Income)" section of our 2017 Financial Report for additional information. Similarly, we have defined the Adjusted income components as *Cost of sales, Selling, informational and administrative expenses, Research and development expenses, Amortization of intangible assets* and *Other (income)/deductions—net* each before the impact of purchase accounting for acquisitions, acquisition-related costs and certain significant items. We have defined Adjusted diluted earnings per share as *Earnings per common share attributable to Pfizer Inc.—diluted* before the impact of purchase accounting for acquisitions, acquisition-related costs, discontinued operations and certain significant items. The Adjusted income measure, the Adjusted income component measures and the Adjusted diluted earnings per share measure are not, and should not be viewed as, substitutes for U.S. GAAP net income, U.S. GAAP net income components or U.S. GAAP diluted earnings per share.

The following are examples of how the Adjusted income and Adjusted diluted earnings per share measures are utilized:

- senior management receives a monthly analysis of our operating results that is prepared on an Adjusted income and Adjusted diluted earnings per share basis;
- our annual budgets are prepared on an Adjusted income and Adjusted diluted earnings per share basis; and
- senior management's annual compensation is derived, in part, using Adjusted income and Adjusted diluted earnings per share measures.

See the "Non-GAAP Financial Measure (Adjusted Income)—General Description of Non-GAAP Financial Measure (Adjusted Income)" section of our 2017 Financial Report for additional information.

Adjusted income and its components and Adjusted diluted earnings per share are non-GAAP financial measures that have no standardized meaning prescribed by U.S. GAAP and, therefore, are limited in their usefulness to investors. Because of their

non-standardized definitions, Adjusted income and its components (unlike U.S. GAAP net income and its components) and Adjusted diluted earnings per share (unlike U.S. GAAP diluted earnings per share) may not be comparable to the calculation of similar measures of other companies. Adjusted income and its components and Adjusted diluted earnings per share are presented solely to permit investors to more fully understand how management assesses performance.

We also recognize that, as internal measures of performance, the Adjusted income and its components and Adjusted diluted earnings per share measures have limitations, and we do not restrict our performance-management process solely to these metrics. A limitation of these measures is that they provide a view of our operations without including all events during a period, such as the effects of an acquisition or amortization of purchased intangibles, and do not provide a comparable view of our performance to other companies in the biopharmaceutical industry. We also use other specifically tailored tools designed to achieve the highest levels of performance. For example, our R&D organization has productivity targets, upon which its effectiveness is measured. In addition, total shareholder return, both on an absolute basis and relative to a publicly-traded pharmaceutical index, plays a significant role in determining payouts under certain of Pfizer's long-term incentive compensation plans.

See the accompanying reconciliations of certain GAAP reported to non-GAAP adjusted information for the third quarter and first nine months of 2018 and 2017 below.

Purchase Accounting Adjustments

Adjusted income is calculated prior to considering certain significant purchase accounting impacts resulting from business combinations and net asset acquisitions. These impacts, primarily associated with Wyeth (acquired in 2009), Hospira (acquired in 2015), Anacor (acquired in June 2016) and Medivation (acquired in September 2016), can include the incremental charge to cost of sales from the sale of acquired inventory that was written up to fair value, amortization related to the increase in fair value of the acquired finite-lived intangible assets, and to a much lesser extent, depreciation related to the increase/decrease in fair value of the acquired fixed assets (primarily manufacturing facilities), amortization related to the increase in fair value of acquired debt, and the fair value changes associated with contingent consideration. Therefore, the Adjusted income measure includes the revenues earned upon the sale of the acquired products without considering the acquisition cost of those products.

Acquisition-Related Costs

Adjusted income is calculated prior to considering transaction, integration, restructuring and additional depreciation costs associated with business combinations because these costs are unique to each transaction and represent costs that were incurred to restructure and integrate two businesses as a result of the acquisition decision. For additional clarity, only transaction costs, additional depreciation and restructuring and integration activities that are associated with a business combination or a net-asset acquisition are included in acquisition-related costs. We have made no adjustments for the resulting synergies.

Discontinued Operations

Adjusted income is calculated prior to considering the results of operations included in discontinued operations, as well as any related gains or losses on the disposal of such operations.

Certain Significant Items

Adjusted income is calculated prior to considering certain significant items. Certain significant items represent substantive and/or unusual items that are evaluated on an individual basis. Such evaluation considers both the quantitative and the qualitative aspects of their nature. Certain significant items may be highly variable and difficult to predict. Furthermore, in some cases it is reasonably possible that they could reoccur in future periods. For example, major non-acquisition-related cost-reduction programs stand on their own as they are specific to an event or goal with a defined term, but we may have subsequent programs based on reorganizations of the business, cost productivity or in response to loss of exclusivity or economic conditions. Legal charges to resolve litigation are also related to specific cases, which are facts and circumstances specific and, in some cases, may also be the result of litigation matters at acquired companies that were inestimable, not probable or unresolved at the date of acquisition. Unusual items may represent items that are not part of our ongoing business; items that, either as a result of their nature or size, we would not expect to occur as part of our normal business on a regular basis; items that would be non-recurring; or items that relate to products we no longer sell. While not all-inclusive, examples of items that could be included as certain significant items would be a major non-acquisition-related restructuring charge and associated implementation costs; amounts related to certain disposals of businesses, products or facilities that do not qualify as discontinued operations under U.S. GAAP; certain intangible asset impairments; adjustments related to the resolution of certain tax positions; the impact of adopting certain significant, event-driven tax legislation, such as the TCJA discussed in Notes to Condensed Consolidated Financial Statements— *Note 5A. Tax Matters: Taxes on Income from Continuing Operations* ; or charges related to certain legal matters, such as certain of those discussed in Notes to Condensed Consolidated Financial Statements— *Note 12A. Contingencies*

and Certain Commitments : Legal Proceedings, included in Part I, Item 1 of this Quarterly Report on Form 10-Q. Normal, ongoing defense costs of the Company or settlements of and accruals for legal matters made in the normal course of our business would not be considered certain significant items.

Reconciliations of GAAP Reported to Non-GAAP Adjusted Information—Certain Line Items

IN MILLIONS, EXCEPT PER COMMON SHARE DATA	Three Months Ended September 30, 2018					
	GAAP Reported	Purchase Accounting Adjustments [a]	Acquisition-Related Costs [a]	Discontinued Operations [a]	Certain Significant Items [a]	Non-GAAP Adjusted
Revenues	**$ 13,298**	$ —	$ —	$ —	$ —	$ 13,298
Cost of sales	**2,694**	1	(3)	—	(19)	2,673
Selling, informational and administrative expenses	**3,494**	—	—	—	(23)	3,471
Research and development expenses	**2,008**	1	—	—	(11)	1,998
Amortization of intangible assets	**1,253**	(1,182)	—	—	—	71
Restructuring charges and certain acquisition-related costs	**85**	—	(107)	—	22	—
Other (income)/deductions—net	**(414)**	(130)	(2)	—	244	(302)
Income from continuing operations before provision for taxes on income	**4,177**	1,309	112	—	(213)	5,386
Provision for taxes on income [b]	**66**	263	21	—	367	716
Income from continuing operations	**4,111**	1,047	91	—	(580)	4,669
Discontinued operations—net of tax	**11**	—	—	(11)	—	—
Net income attributable to noncontrolling interests	**8**	—	—	—	—	8
Net income attributable to Pfizer Inc.	**4,114**	1,047	91	(11)	(580)	4,661
Earnings per common share attributable to Pfizer Inc.—diluted	**0.69**	0.17	0.02	—	(0.10)	0.78

IN MILLIONS, EXCEPT PER COMMON SHARE DATA	Nine Months Ended September 30, 2018					
	GAAP Reported	Purchase Accounting Adjustments [a]	Acquisition-Related Costs [a]	Discontinued Operations [a]	Certain Significant Items [a]	Non-GAAP Adjusted
Revenues	**$ 39,670**	$ —	$ —	$ —	$ —	$ 39,670
Cost of sales	**8,173**	(2)	(9)	—	(77)	8,086
Selling, informational and administrative expenses	**10,448**	1	—	—	(185)	10,264
Research and development expenses	**5,549**	3	—	—	(26)	5,526
Amortization of intangible assets	**3,640**	(3,428)	—	—	—	212
Restructuring charges and certain acquisition-related costs	**172**	—	(209)	—	37	—
Other (income)/deductions—net	**(1,143)**	(238)	(4)	—	242	(1,143)
Income from continuing operations before provision for taxes on income	**12,831**	3,665	221	—	8	16,725
Provision for taxes on income [b]	**1,270**	735	40	—	500	2,544
Income from continuing operations	**11,562**	2,930	182	—	(492)	14,181
Discontinued operations—net of tax	**10**	—	—	(10)	—	—
Net income attributable to noncontrolling interests	**25**	—	—	—	—	25
Net income attributable to Pfizer Inc.	**11,546**	2,930	182	(10)	(492)	14,156
Earnings per common share attributable to Pfizer Inc.—diluted	**1.92**	0.49	0.03	—	(0.08)	2.36

See end of tables for notes [a] and [b].

IN MILLIONS, EXCEPT PER COMMON SHARE DATA	Three Months Ended October 1, 2017					
	GAAP Reported	Purchase Accounting Adjustments [a]	Acquisition-Related Costs [a]	Discontinued Operations [a]	Certain Significant Items [a]	Non-GAAP Adjusted
Revenues	**$ 13,168**	$ —	$ —	$ —	$ —	$ 13,168
Cost of sales	**2,844**	(28)	(26)	—	(92)	2,696
Selling, informational and administrative expenses	**3,504**	—	—	—	(22)	3,482
Research and development expenses	**1,865**	1	—	—	(9)	1,857
Amortization of intangible assets	**1,177**	(1,120)	—	—	—	57
Restructuring charges and certain acquisition-related costs	**114**	—	(129)	—	15	—
Other (income)/deductions—net	**79**	(7)	—	—	(340)	(268)
Income from continuing operations before provision for taxes on income	**3,585**	1,154	155	—	449	5,343
Provision for taxes on income [b]	**727**	306	72	—	161	1,267
Income from continuing operations	**2,858**	848	83	—	288	4,077
Discontinued operations—net of tax	**—**	—	—	—	—	—
Net income attributable to noncontrolling interests	**18**	—	—	—	—	18
Net income attributable to Pfizer Inc.	**2,840**	848	83	—	288	4,059
Earnings per common share attributable to Pfizer Inc.—diluted	**0.47**	0.14	0.01	—	0.05	0.67

IN MILLIONS, EXCEPT PER COMMON SHARE DATA	Nine Months Ended October 1, 2017					
	GAAP Reported	Purchase Accounting Adjustments [a]	Acquisition-Related Costs [a]	Discontinued Operations [a]	Certain Significant Items [a]	Non-GAAP Adjusted
Revenues	**$ 38,843**	$ —	$ —	$ —	$ —	$ 38,843
Cost of sales	**7,972**	(45)	(38)	—	(168)	7,720
Selling, informational and administrative expenses	**10,249**	(15)	—	—	(67)	10,167
Research and development expenses	**5,367**	7	—	—	(26)	5,348
Amortization of intangible assets	**3,571**	(3,438)	—	—	—	133
Restructuring charges and certain acquisition-related costs	**267**	—	(319)	—	52	—
Other (income)/deductions—net	**65**	(35)	10	—	(588)	(547)
Income from continuing operations before provision for taxes on income	**11,351**	3,527	347	—	797	16,023
Provision for taxes on income [b]	**2,287**	990	137	—	263	3,677
Income from continuing operations	**9,064**	2,537	211	—	534	12,345
Discontinued operations—net of tax	**1**	—	—	(1)	—	—
Net income attributable to noncontrolling interests	**32**	—	—	—	—	32
Net income attributable to Pfizer Inc.	**9,034**	2,537	211	(1)	534	12,313
Earnings per common share attributable to Pfizer Inc.—diluted	**1.49**	0.42	0.03	—	0.09	2.03

[a] For details of adjustments, see "Details of Income Statement Items Included in GAAP Reported but Excluded from Non-GAAP Adjusted Income" below.

[b] The effective tax rate on Non-GAAP Adjusted income was 13.3% in the third quarter of 2018 , compared to 23.7% in the third quarter of 2017 . The effective tax rate on Non-GAAP Adjusted income was 15.2% in the first nine months of 2018 , compared to 22.9% in the first nine months of 2017 . The decreases were primarily due to tax benefits associated with the December 2017 enactment of the TCJA, a favorable change in the jurisdictional mix of earnings as a result of operating fluctuations in the normal course of business, as well as an increase in benefits associated with the resolution of certain tax positions pertaining to prior years primarily with various foreign tax authorities, and the expiration of certain statutes of limitations.

Details of Income Statement Items Included in GAAP Reported but Excluded from Non-GAAP Adjusted Income

(MILLIONS OF DOLLARS)	Three Months Ended		Nine Months Ended	
	September 30, 2018	October 1, 2017	September 30, 2018	October 1, 2017
Purchase accounting adjustments				
Amortization, depreciation and other [a]	$ 1,310	$ 1,126	$ 3,662	$ 3,482
Cost of sales	(1)	28	2	45
Total purchase accounting adjustments—pre-tax	1,309	1,154	3,665	3,527
Income taxes [b]	(263)	(306)	(735)	(990)
Total purchase accounting adjustments—net of tax	1,047	848	2,930	2,537
Acquisition-related costs				
Restructuring charges [c]	24	70	5	80
Transaction costs [c]	1	(14)	1	4
Integration costs [c]	82	73	202	235
Net periodic benefit costs/(credits) other than service costs [d]	2	—	4	(10)
Additional depreciation—asset restructuring [e]	3	26	9	38
Total acquisition-related costs—pre-tax	112	155	221	347
Income taxes [f]	(21)	(72)	(40)	(137)
Total acquisition-related costs—net of tax	91	83	182	211
Discontinued operations				
Total discontinued operations—net of tax, attributable to Pfizer Inc. [g]	(11)	—	(10)	(1)
Certain significant items				
Restructuring credits — cost reduction initiatives [h]	(22)	(15)	(37)	(52)
Implementation costs and additional depreciation—asset restructuring [i]	57	69	164	185
Certain legal matters, net [j]	37	183	(70)	191
Adjustments to loss on sale of HIS net assets [j]	(2)	(12)	(1)	52
Certain asset impairments [j]	—	127	31	127
Business and legal entity alignment costs [j]	—	16	4	54
Other [k]	(282)	81	(84)	239
Total certain significant items—pre-tax	(213)	449	8	797
Income taxes [l]	(367)	(161)	(500)	(263)
Total certain significant items—net of tax	(580)	288	(492)	534
Total purchase accounting adjustments, acquisition-related costs, discontinued operations and certain significant items—net of tax, attributable to Pfizer Inc.	$ 547	$ 1,219	$ 2,610	$ 3,280

[a] Included primarily in *Amortization of intangible assets.*

[b] Included in *Provision for taxes on income.* Income taxes includes the tax effect of the associated pre-tax amounts, calculated by determining the jurisdictional location of the pre-tax amounts and applying that jurisdiction's applicable tax rate.

[c] Included in *Restructuring charges and certain acquisition-related costs* . Restructuring charges include employee termination costs, asset impairments and other exit costs associated with business combinations. Restructuring charges for the three months ended September 30, 2018 were primarily due to accruals for exit costs and asset write downs related to our acquisition of Hospira , and charges for the nine months ended September 30, 2018 were primarily due to asset write downs related to our acquisition of Hospira, partially offset by the reversal of previously recorded accruals for employee termination costs related to our acquisition of Hospira. Restructuring charges for the third quarter and first nine months of 2017 were mainly related to our acquisitions of Hospira and Medivation . Transaction costs represent external costs for banking, legal, accounting and other similar services. Integration costs represent external, incremental costs directly related to integrating acquired businesses, and primarily include expenditures for consulting and the integration of systems and processes. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives* .

[d] Amounts for the three and nine months ended October 1, 2017 represent the net periodic benefit credits, excluding service costs, reclassified to *Other (income)/deductions—net* as a result of the retrospective adoption of a new accounting standard in the first quarter of 2018. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 1B. Basis of Presentation and Significant Accounting Policies: Adoption of New Accounting Standards.* These credits included a net settlement gain, partially offset by accelerated amortization of actuarial losses and prior service costs upon the settlement of the remaining obligation associated with the Hospira U.S. qualified defined benefit pension plan.

[e] Included in *Cost of sales.* Represents the impact of changes in estimated useful lives of assets involved in restructuring actions related to acquisitions.

[f] Included in *Provision for taxes on income* . Income taxes includes the tax effect of the associated pre-tax amounts, calculated by determining the jurisdictional location of the pre-tax amounts and applying that jurisdiction's applicable tax rate.

[g] Included in *Discontinued operations—net of tax.*

[h] Amounts relate to employee termination costs, asset impairments and other exit costs not associated with acquisitions, which are included in *Restructuring charges and certain acquisition-related cost* (see Notes to Condensed Consolidated Financial Statements— *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives*). For the three and nine months ended September 30, 2018 and October 1, 2017 , the credits are mostly related to the reversal of previously recorded accruals for employee termination costs.

[i] Amounts relate to our cost-reduction/productivity initiatives not related to acquisitions (see Notes to Condensed Consolidated Financial Statements— *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives*). For the three months ended September 30, 2018 , included in *Cost of sales* ($30 million), *Selling, informational and administrative expenses* ($17 million) and *Research and development expenses* ($9 million). For the three months ended October 1, 2017 , included in *Cost of sales* ($38 million), *Selling, informational and administrative expenses* ($22 million) and *Research and development expenses* ($9 million). For the nine months ended September 30, 2018 , included in *Cost of sales* ($91 million), *Selling, informational and administrative expenses* ($51 million) and *Research and development expenses* ($22 million). For the nine months ended October 1, 2017 , included in *Cost of sales* ($113 million), *Selling, informational and administrative expenses* ($46 million) and *Research and development expenses* ($26 million).

[j] Included in *Other (income)/deductions — net* (see Notes to Condensed Consolidated Financial Statements— *Note 4. Other (Income)/Deductions—Net*) .

[k] For the three months ended September 30, 2018 , primarily included in *Cost of sales* ($12 million income *), Selling, informational and administrative expenses* ($6 million) and *Other (income)/deductions—net* ($279 million income). For the nine months ended September 30, 2018 , primarily included in *Cost of sales* ($14 million income *), Selling, informational and administrative expenses* ($134 million) and *Other (income)/deductions—net* ($206 million income). For the third quarter and first nine months of 2018, includes, among other things, a non-cash $343 million pre-tax gain in *Other (income)/deductions—net* associated with our transaction with Bain Capital to create a new biopharmaceutical company, Cerevel, to continue development of a portfolio of clinical and preclinical stage neuroscience assets primarily targeting disorders of the central nervous system. The first nine months of 2018 also includes (i) a $119 million charge, in the aggregate, in *Selling, informational and administrative expenses* for a special, one-time bonus paid to virtually all Pfizer colleagues, excluding executives, which was one of several actions taken by us after evaluating the expected positive net impact of the December 2017 enactment of the legislation commonly referred to as the TCJA on us and (ii) a non-cash $50 million pre-tax gain in *Other (income)/deductions—net* as a result of the contribution of our allogeneic chimeric antigen receptor T cell therapy development program assets in connection with our contribution agreement entered into with Allogene (see Notes to Condensed Consolidated Financial Statements— *Note 2B. Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment : Divestitures*) . For the three months ended October 1, 2017 , included in *Cost of sales* ($54 million) and *Other (income)/deductions—net* ($26 million). For the nine months ended October 1, 2017 , included in *Cost of sales* ($55 million), *Selling, informational and administrative expenses* ($21 million) and *Other (income)/deductions—net* ($163 million). For the third quarter and first nine months of 2017 , includes $55 million in inventory losses, overhead costs related to the period in which our Puerto Rico plants were not operational, and incremental costs, all of which resulted from hurricanes in Puerto Rico and are included in *Cost of sales* . For the nine months ended October 1, 2017 , also includes a net loss of $30 million related to the sale of our 40% ownership investment in Teuto, including the extinguishment of a put option for the then remaining 60% ownership interest, which is included in *Other (income)/deductions—net.*

[l] Included in *Provision for taxes on income* . Income taxes includes the tax effect of the associated pre-tax amounts, calculated by determining the jurisdictional location of the pre-tax amounts and applying that jurisdiction's applicable tax rate. The three months and nine months ended September 30, 2018 were favorably impacted by the December 2017 enactment of the TCJA, primarily related to certain tax initiatives, as well as favorable adjustments to the provisional estimate of the impact of the legislation. Given the significant changes resulting from and complexities associated with the TCJA, the estimated financial impacts recorded in 2017 remain provisional and are subject to further analysis, interpretation and clarification of the TCJA, which could result in further changes to these estimates in the fourth quarter of 2018. Under guidance issued by the staff of the SEC, we expect to finalize our accounting related to the tax effects of the TCJA on deferred taxes, valuation allowances, state tax considerations, the repatriation tax liability, global intangible low-taxed income, and any remaining outside basis differences in our foreign subsidiaries during the fourth quarter of 2018, as we complete the remainder of our tax return filings and as any interpretations or clarifications of the TCJA occur through legislation or U.S. Treasury actions or other means.

ANALYSIS OF OPERATING SEGMENT INFORMATION

The following tables and associated notes provide additional information about the performance of our two operating segments—the IH segment and the EH segment. For additional information about each operating segment, see the "Our Strategy — Commercial Operations" section of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 13. Segment, Geographic and Other Revenue Information ,* as well as the "Selected Balance Sheet Information by Operating Segment" section of the MD&A in our Quarterly Report on Form 10-Q for the quarterly period ended April 1, 2018.

As described in the Notes to Condensed Consolidated Financial Statements— *Note 1A. Basis of Presentation and Significant Accounting Policies : Basis of Presentation* , the February 3, 2017 sale of HIS impacted our results of operations in 2017.

The following tables provide revenue and cost information by reportable operating segment and a reconciliation of that information to our condensed consolidated statements of income:

	Third Quarter of 2018					
(MILLIONS OF DOLLARS)	Innovative Health (IH) [a]	Essential Health (EH) [a]	Other [b]	Non-GAAP Adjusted [c]	Reconciling Items [d]	**GAAP Reported**
Revenues	$ 8,471	$ 4,826	$ —	$ 13,298	$ —	**$ 13,298**
Cost of sales	981	1,413	279	2,673	21	**2,694**
% of revenue	11.6%	29.3%	*	20.1%	*	**20.3%**
Selling, informational and administrative expenses	1,695	663	1,114	3,471	23	**3,494**
Research and development expenses	695	225	1,078	1,998	10	**2,008**
Amortization of intangible assets	57	20	(6)	71	1,182	**1,253**
Restructuring charges and certain acquisition-related costs	—	—	—	—	85	**85**
Other (income)/deductions—net	(345)	(22)	65	(302)	(112)	**(414)**
Income/(loss) from continuing operations before provision for taxes on income	$ 5,388	$ 2,527	$ (2,530)	$ 5,386	$ (1,208)	**$ 4,177**

	Nine Months Ended September 30, 2018					
(MILLIONS OF DOLLARS)	Innovative Health (IH) [a]	Essential Health (EH) [a]	Other [b]	Non-GAAP Adjusted [c]	Reconciling Items [d]	**GAAP Reported**
Revenues	$ 24,573	$ 15,097	$ —	$ 39,670	$ —	**$ 39,670**
Cost of sales	3,049	4,442	595	8,086	87	**8,173**
% of revenue	12.4%	29.4%	*	20.4%	*	**20.6%**
Selling, informational and administrative expenses	4,967	1,909	3,388	10,264	183	**10,448**
Research and development expenses	1,882	683	2,961	5,526	23	**5,549**
Amortization of intangible assets	165	47	—	212	3,428	**3,640**
Restructuring charges and certain acquisition-related costs	—	—	—	—	172	**172**
Other (income)/deductions—net	(909)	(117)	(117)	(1,143)	—	**(1,143)**
Income/(loss) from continuing operations before provision for taxes on income	$ 15,419	$ 8,133	$ (6,827)	$ 16,725	$ (3,894)	**$ 12,831**

	Third Quarter of 2017					
(MILLIONS OF DOLLARS)	Innovative Health (IH) [a]	Essential Health (EH) [a]	Other [b]	Non-GAAP Adjusted [c]	Reconciling Items [d]	**GAAP Reported**
Revenues	$ 8,118	$ 5,050	$ —	$ 13,168	$ —	**$ 13,168**
Cost of sales	1,082	1,448	167	2,696	147	**2,844**
% of revenue	13.3%	28.7%	*	20.5%	*	**21.6%**
Selling, informational and administrative expenses	1,619	693	1,171	3,482	22	**3,504**
Research and development expenses	634	250	973	1,857	8	**1,865**
Amortization of intangible assets	40	17	—	57	1,120	**1,177**
Restructuring charges and certain acquisition-related costs	—	—	—	—	114	**114**
Other (income)/deductions—net	(256)	(158)	147	(268)	347	**79**
Income/(loss) from continuing operations before provision for taxes on income	$ 5,000	$ 2,801	$ (2,457)	$ 5,343	$ (1,759)	**$ 3,585**

See end of tables for notes (a) through (d).

(MILLIONS OF DOLLARS)	Nine Months Ended October 1, 2017					
	Innovative Health (IH) [a]	Essential Health (EH) [a]	Other [b]	Non-GAAP Adjusted [c]	Reconciling Items [d]	**GAAP Reported**
Revenues	$ 23,204	$ 15,639	$ —	$ 38,843	$ —	**$ 38,843**
Cost of sales	2,912	4,319	489	7,720	252	**7,972**
% of revenue	12.6%	27.6%	*	19.9%	*	**20.5%**
Selling, informational and administrative expenses	4,598	2,103	3,467	10,167	82	**10,249**
Research and development expenses	1,694	760	2,894	5,348	20	**5,367**
Amortization of intangible assets	90	43	—	133	3,438	**3,571**
Restructuring charges and certain acquisition-related costs	—	—	—	—	267	**267**
Other (income)/deductions—net	(623)	(258)	334	(547)	613	**65**
Income/(loss) from continuing operations before provision for taxes on income	$ 14,534	$ 8,672	$ (7,183)	$ 16,023	$ (4,671)	**$ 11,351**

* Indicates calculation not meaningful or result is equal to or greater than 100%.

[a] Amounts represent the revenues and costs managed by each of our operating segments. The expenses generally include only those costs directly attributable to the operating segment.

The following organizational change impacted our operating segments in 2018:

Effective in the first quarter of 2018, certain costs for Pfizer's StratCO group, which were previously reported in the operating results of our operating segments and Corporate, are reported in Other Unallocated. StratCO costs primarily include headcount costs, vendor costs and data costs largely in support of Pfizer's commercial operations. The majority of the StratCO costs reflect additional amounts that our operating segments would have incurred had each segment operated as a standalone company during the periods presented. The reporting change was made to streamline accountability and speed decision making. In the third quarter of 2017, we reclassified approximately $125 million of costs from IH, approximately $36 million of costs from EH and approximately $19 million of costs from Corporate to Other unallocated costs to conform to the current period presentation. In the first nine months of 2017, we reclassified approximately $344 million of costs from IH, approximately $114 million of costs from EH and approximately $40 million of costs from Corporate to Other unallocated costs to conform to the current period presentation.

[b] Other comprises the costs included in our Adjusted income components (see footnote (c) below) that are managed outside of our two operating segments and includes the following:

(MILLIONS OF DOLLARS)	Third Quarter of 2018				
	Other Business Activities				
	WRD [i]	GPD [ii]	Corporate [iii]	Other Unallocated [iv]	Total
Revenues	$ —	$ —	$ —	$ —	$ —
Cost of sales	—	—	21	258	279
Selling, informational and administrative expenses	—	—	950	164	1,114
Research and development expenses	550	193	318	16	1,078
Amortization of intangible assets	—	—	—	(6)	(6)
Restructuring charges and certain acquisition-related costs	—	—	—	—	—
Other (income)/deductions—net	(6)	(1)	47	26	65
Loss from continuing operations before provision for taxes on income	$ (543)	$ (192)	$ (1,337)	$ (457)	$ (2,530)

(MILLIONS OF DOLLARS)	Nine Months Ended September 30, 2018				
	Other Business Activities				
	WRD [i]	GPD [ii]	Corporate [iii]	Other Unallocated [iv]	Total
Revenues	$ —	$ —	$ —	$ —	$ —
Cost of sales	—	—	149	446	595
Selling, informational and administrative expenses	—	—	2,881	507	3,388
Research and development expenses	1,664	579	672	46	2,961
Amortization of intangible assets	—	—	—	—	—
Restructuring charges and certain acquisition-related costs	—	—	—	—	—
Other (income)/deductions—net	(110)	(4)	(69)	65	(117)
Loss from continuing operations before provision for taxes on income	$ (1,554)	$ (575)	$ (3,633)	$ (1,064)	$ (6,827)

	Third Quarter of 2017				
	Other Business Activities				
(MILLIONS OF DOLLARS)	WRD [i]	GPD [ii]	Corporate [iii]	Other Unallocated [iv]	Total
Revenues	$ —	$ —	$ —	$ —	$ —
Cost of sales	—	—	27	139	167
Selling, informational and administrative expenses	—	—	980	191	1,171
Research and development expenses	570	195	189	20	973
Amortization of intangible assets	—	—	—	—	—
Restructuring charges and certain acquisition-related costs	—	—	—	—	—
Other (income)/deductions—net	(4)	(1)	167	(15)	147
Loss from continuing operations before provision for taxes on income	$ (566)	$ (193)	$ (1,363)	$ (335)	$ (2,457)

	Nine Months Ended October 1, 2017				
	Other Business Activities				
(MILLIONS OF DOLLARS)	WRD [i]	GPD [ii]	Corporate [iii]	Other Unallocated [iv]	Total
Revenues	$ —	$ —	$ —	$ —	$ —
Cost of sales	—	—	(4)	493	489
Selling, informational and administrative expenses	—	(1)	2,965	502	3,467
Research and development expenses	1,680	565	609	39	2,894
Amortization of intangible assets	—	—	—	—	—
Restructuring charges and certain acquisition-related costs	—	—	—	—	—
Other (income)/deductions—net	(36)	(4)	338	36	334
Loss from continuing operations before provision for taxes on income	$ (1,644)	$ (561)	$ (3,908)	$ (1,070)	$ (7,183)

[i] WRD—the R&D expenses managed by our WRD organization, which is generally responsible for research projects for our IH business until proof-of-concept is achieved and then for transitioning those projects to the IH segment via the GPD organization for possible clinical and commercial development. R&D spending may include upfront and milestone payments for intellectual property rights. The WRD organization also has responsibility for certain science-based and other platform-services organizations, which provide technical expertise and other services to the various R&D projects, including EH R&D projects. WRD is also responsible for facilitating all regulatory submissions and interactions with regulatory agencies, including all safety-event activities.

[ii] GPD — the costs associated with our GPD organization, which is generally responsible for the clinical development of assets that are in clinical trials for our WRD and Innovative portfolios. GPD also provides technical support and other services to Pfizer R&D projects.

[iii] Corporate—the costs associated with Corporate, representing platform functions (such as worldwide technology, global real estate operations, legal, finance, human resources, worldwide public affairs, compliance and worldwide procurement), the provision of medical information to healthcare providers, patients and other parties, transparency and disclosure activities, clinical trial results publication, grants for healthcare quality improvement and medical education, and partnerships with global public health and medical associations, as well as certain compensation and other corporate costs, such as interest income and expense, and gains and losses on investments. Effective in the first quarter of 2018, certain costs for StratCO, which were previously reported in the operating results of our operating segments and Corporate, are reported in Other Unallocated. For additional information, see note (iv) below.

We recognized a $14 million loss in the third quarter of 2018 and a $47 million gain in the first nine months of 2018 as an offset to *Cost of sales* primarily related to euro-denominated forward-exchange contracts designated as cash flow hedges of a portion of our foreign exchange-denominated forecasted intercompany inventory sales. We recognized a $4 million loss in the third quarter of 2017 and a $67 million gain in the first nine months of 2017 as a reduction to *Cost of sales* related to euro, Japanese yen and U.K. pound-denominated forward-exchange contracts designated as cash flow hedges of a portion of our foreign exchange-denominated forecasted intercompany inventory sales. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 7F. Financial Instruments* : *Derivative Financial Instruments and Hedging Activities* .

[iv] Other Unallocated—other unallocated costs, representing overhead expenses associated with our manufacturing and commercial operations that are not directly assessed to an operating segment, as business unit (segment) management does not manage these costs (which include manufacturing variances associated with production). In connection with the StratCO reporting change, in the third quarter of 2017, we reclassified approximately $125 million of costs from IH, approximately $36 million of costs from EH and approximately $19 million of costs from Corporate to Other unallocated costs to conform to the current period presentation. In the first nine months of 2017, we reclassified approximately $344 million of costs from IH, approximately $114 million of costs from EH and approximately $40 million of costs from Corporate to Other unallocated costs to conform to the current period presentation.

For information purposes only, the following tables present reconciliations of our segment operating results to segment operating results including estimated Other costs generally associated with each segment. While we do not manage our segments or have performance goals under such an allocated manner, we believe that some investors may find this information useful in their analyses.

The estimated Other costs generally associated with our operating segments do not purport to reflect the additional amounts that each of our operating segments would have incurred had each segment operated as a standalone company during the period presented.

For information purposes only, for the first nine months of 2018 , we estimate that Other costs, as described above, for combined WRD and GPD costs of $2.1 billion , and combined Corporate and Other Unallocated costs of $4.4 billion after excluding (i) net interest-related expense not attributable to an operating segment included in Corporate (approximately $730 million for the first nine months of 2018 in *Other (income)/deductions—net*); and (ii) net income from investments and other assets not attributable to an operating segment included in Corporate (approximately $442 million for the first nine months of 2018 in *Other (income)/deductions—net*), are generally associated with our operating segments, as follows:

	Nine Months Ended September 30, 2018			
		Estimated Other Costs Associated with IH [ii]		
(MILLIONS OF DOLLARS)	Innovative Health Non-GAAP Adjusted [i], [iii]	Estimated WRD/GPD [ii]	Estimated Corporate/Other Unallocated [ii]	Innovative Health with Estimated Other Costs Associated with Innovative Health Non-GAAP Adjusted [ii], [iii]
Revenues	$ 24,573	$ —	$ —	$ 24,573
Cost of sales	3,049	—	81	3,130
Selling, informational and administrative expenses	4,967	—	1,918	6,886
Research and development expenses	1,882	2,219	658	4,760
Amortization of intangible assets	165	—	(4)	161
Restructuring charges and certain acquisition-related costs	—	—	—	—
Other (income)/deductions—net	(909)	(113)	(213)	(1,235)
Income from continuing operations before provision for taxes on income	15,419	(2,106)	(2,441)	10,872

	Nine Months Ended September 30, 2018			
		Estimated Other Costs Associated with EH [ii]		
(MILLIONS OF DOLLARS)	Essential Health Non-GAAP Adjusted [i], [iii]	Estimated WRD/GPD [ii]	Estimated Corporate/Other Unallocated [ii]	Essential Health with Estimated Other Costs Associated with Essential Health Non-GAAP Adjusted [ii], [iii]
Revenues	$ 15,097	$ —	$ —	$ 15,097
Cost of sales	4,442	—	514	4,956
Selling, informational and administrative expenses	1,909	—	1,469	3,379
Research and development expenses	683	24	60	767
Amortization of intangible assets	47	—	4	51
Restructuring charges and certain acquisition-related costs	—	—	—	—
Other (income)/deductions—net	(117)	—	(78)	(195)
Income from continuing operations before provision for taxes on income	8,133	(24)	(1,969)	6,141

[i] Amount represents the revenues and costs managed by each of our operating segments. The expenses generally include only those costs directly attributable to the operating segment. See note (a) above for more information.

[ii] Represents costs not assessed to an operating segment, as business unit (segment) management does not manage these costs. For a description of these other costs and business activities, see note (b) above.

- WRD/GPD — The information provided for WRD and GPD was substantially all derived from our estimates of the costs incurred in connection with the R&D projects associated with each operating segment.
- Corporate/Other Unallocated — The information provided for Corporate and Other Unallocated was derived mainly using proportional allocation methods based on global, regional or country revenues or global, regional or country headcount, as well as certain cost metrics, as appropriate, such as those derived from research and development and manufacturing costs, and, to a lesser extent, specific identification and estimates. Management believes that the allocations of Corporate and Other Unallocated costs are reasonable.

The estimated Other costs generally associated with our operating segments do not purport to reflect the additional amounts that each of our operating segments would have incurred had each segment operated as a standalone company during the period presented.

[iii] See note (c) below for an explanation of our Non-GAAP Adjusted financial measure.

[c] See the "Non-GAAP Financial Measure (Adjusted Income)" section of this MD&A for a definition of these "Adjusted Income" components.

[d] Includes costs associated with (i) purchase accounting adjustments; (ii) acquisition-related costs; and (iii) certain significant items, which are substantive and/or unusual, and in some cases recurring, items (such as restructuring or legal charges), that are evaluated on an individual basis by management. For additional information about these reconciling items and/or our Non-GAAP adjusted measure of performance, see the "Non-GAAP Financial Measure (Adjusted Income)" section of this MD&A.

Third Quarter of 2018 vs. Third Quarter of 2017

Innovative Health Operating Segment

Revenues

IH *Revenues* increase d $353 million , or 4% , to $8.5 billion , reflecting an operational increase of $426 million , or 5% , partially offset by the unfavorable impact of foreign exchange of $73 million , or 1% .

The following provides an analysis of the increase in IH worldwide *Revenues* :

(MILLIONS OF DOLLARS)		
IH *Revenues* , for the three months ended October 1, 2017	$	8,118
Operational growth/(decline):		
Continued growth from certain key brands [(a)]		660
Growth from recently launched products, including Eucrisa in the U.S., as well as Besponsa and Bavencio, primarily in the U.S. and developed Europe		52
Negative impact of the loss of exclusivity of Viagra in the U.S. in December 2017 and the resulting shift in the reporting of U.S. and Canada Viagra revenues from IH to EH at the beginning of 2018		(206)
Lower revenues for Enbrel, primarily in most developed Europe markets due to continued biosimilar competition		(65)
Other operational factors, net		(15)
Operational growth, net		426
Unfavorable impact of foreign exchange		(73)
IH *Revenues* increase		353
IH *Revenues* , for the three months ended September 30, 2018	$	8,471

[(a)] Certain k ey brands represent Eliquis, Ibrance, Prevnar 13/Prevenar 13, Xeljanz and Xtandi. See the "Analysis of the Condensed Consolidated Statements of Income—Revenues—Selected Product Discussion" section of this MD&A for product analysis information .

Total IH revenues from emerging markets increase d $78 million , or 7% , to $1.2 billion from $1.1 billion , reflecting 14% operational growth. Foreign exchange had an unfavorable impact of 7% on total IH revenues from emerging markets.

Costs and Expenses

- *Cost of sales* as a percentage of *Revenues* decrease d 1.7 percentage points, primarily driven by the favorable impact of foreign exchange.
- The decrease in *Cost of sales* of 9% was primarily driven by the favorable impact of foreign exchange, partially offset by an increase in sales volumes for various key products within our product portfolio and an increase in royalty expenses based on the mix of products sold.
- The increase in *Selling, informational and administrative expenses* of 5% was primarily driven by additional investment across several of our key products, primarily Xeljanz, Eucrisa, Eliquis and Prevnar 13/Prevenar 13 (pediatric indication), partially offset by lower healthcare reform expenses as a result of a true up of a prior year amount, and the favorable impact of foreign exchange.
- The increase in *Research and development expenses* of 10% primarily reflects:
  - increased costs for our rare disease portfolio;
  - increased costs associated with our Phase 3 clinical trial related to our JAK1 inhibitor (which was initiated in December 2017); and
  - increased costs across the Oncology portfolio, including costs associated with Bavencio studies,

  partially offset by:
  - lower costs due to the completion of certain tanezumab studies.
- The favorable change in *Other (income)/deductions—net* primarily reflects:
  - a $36 million increase in dividend income from our investment in ViiV;
  - a $33 million increase in income from collaborations, out-licensing arrangements and sales of compound/product rights; and
  - a $14 million increase in Xtandi royalty income.

Essential Health Operating Segment

Revenues

EH *Revenues* decrease d $223 million , or 4% , to $4.8 billion , reflecting an operational decrease of $183 million , or 4% , and the unfavorable impact of foreign exchange of $40 million , or 1% .

The following provides an analysis of the decrease in EH worldwide *Revenues* :

(MILLIONS OF DOLLARS)		
EH *Revenues* , for the three months ended October 1, 2017	$	5,050
Operational growth/(decline):		
Decline from the Peri-LOE Products portfolio, driven by lower revenues in developed markets (excluding Viagra EH), primarily due to expected declines in Lyrica in developed Europe		(125)
Decline in the LEP portfolio primarily driven by lower revenues in developed markets		(121)
Decline from the SIP portfolio, driven by lower revenues in developed markets, primarily due to continued legacy Hospira product shortages in the U.S.		(28)
Positive impact of Viagra, mostly driven by the shift in the reporting of U.S. and Canada Viagra revenues from IH to EH at the beginning of 2018 (due to the loss of exclusivity of Viagra in the U.S. in December 2017), partially offset by lower revenues in emerging markets and developed Europe markets (previously reported in EH)		37
Growth from Biosimilars, primarily from Inflectra in certain channels in the U.S., as well as in developed Europe		56
Other operational factors, net		(2)
Operational decline, net		(183)
Unfavorable impact of foreign exchange		(40)
EH *Revenues* decrease		(223)
EH *Revenues* , for the three months ended September 30, 2018	$	4,826

Total EH revenues from emerging markets increase d $149 million , or 9% , to $1.9 billion from $1.7 billion , reflecting 11% operational growth, primarily driven by 11% operational growth from the LEP portfolio and 14% operational growth from the SIP portfolio, partially offset by a 2% operational decline from the Peri-LOE Products portfolio. Foreign exchange had an unfavorable impact of 3% on total EH revenues from emerging markets.

Costs and Expenses

- *Cost of sales* as a percentage of *Revenues* increase d 0.6 percentage points, primarily due to:
  - higher sales volumes of Inflectra in the U.S. and developed Europe, which carry higher product costs; and
  - lower sales volumes and margins as a result of product losses of exclusivity and generic competition in developed markets,

  partially offset by:
  - the favorable impact of foreign exchange; and
  - lower sales volumes in the SIP portfolio, which carries a higher cost to produce, in developed markets, primarily due to continued legacy Hospira product shortages in the U.S.
- The decrease in *Cost of sales* of 2% was primarily due to:
  - the favorable impact of foreign exchange; and
  - lower sales volumes driven by product losses of exclusivity and generic competition in developed markets,

  partially offset by:
  - higher sales volumes of Inflectra in the U.S. and developed Europe, which carry higher product costs; and
  - higher costs across the SIP portfolio, as a result of the complexity of high quality product manufacturing across the legacy Hospira plants.
- *Selling, informational and administrative expenses* decrease d 4% mainly due to lower general and administrative expenses, as well as lower advertising, promotional and field force expenses, reflecting the benefits of cost-reduction and productivity initiatives, and the favorable impact of foreign exchange, partially offset by additional investments in China .
- *Research and development expenses* decrease d 10% primarily due to decreased spending for biosimilars as several programs have reached completion.
- The unfavorable change in *Other (income)/deductions—net* primarily reflects the non-recurrence of income from resolution of a contract disagreement, the unfavorable impact of foreign exchange and the non-recurrence of a gain on the redemption of an acquired bond in 2017, partially offset by an increase in income from collaborations, out-licensing arrangements and sales of compound/product rights.

First Nine Months of 2018 vs. First Nine Months of 2017

Innovative Health Operating Segment

Revenues

IH *Revenues* increase d $1.4 billion , or 6% , to $24.6 billion , reflecting an operational increase of $1.0 billion , or 4% , and the favorable impact of foreign exchange of $342 million , or 2% .

The following provides an analysis of the increase in IH worldwide *Revenues* :

(MILLIONS OF DOLLARS)		
IH *Revenues* , for the nine months ended October 1, 2017	$	23,204
Operational growth/(decline):		
Continued growth from certain key brands [(a)]		1,835
Growth from recently launched products, including Eucrisa in the U.S., as well as Besponsa and Bavencio, primarily in the U.S. and developed Europe		172
Negative impact of the loss of exclusivity of Viagra in the U.S. in December 2017 and the resulting shift in the reporting of U.S. and Canada Viagra revenues from IH to EH at the beginning of 2018		(711)
Lower revenues for Enbrel, primarily in most developed Europe markets due to continued biosimilar competition		(279)
Other operational factors, net		11
Operational growth, net		1,028
Favorable impact of foreign exchange		342
IH *Revenues* increase		1,370
IH *Revenues* , for the nine months ended September 30, 2018	$	24,573

[(a)]Certain k ey brands represent Eliquis, Ibrance, Xeljanz, Prevnar 13/Prevenar 13, Xtandi and Chantix/Champix. See the "Analysis of the Condensed Consolidated Statements of Income—Revenues—Selected Product Discussion" section of this MD&A for product analysis information.

Total IH revenues from emerging markets increase d $456 million , or 15% , to $3.6 billion from $3.1 billion , reflecting a 16% operational increase . Foreign exchange had an unfavorable impact of 1% on Total IH revenues from emerging markets.

Costs and Expenses

- *Cost of sales* as a percentage of *Revenues* decrease d 0.1 percentage points, primarily driven by the favorable impact of foreign exchange, partially offset by an unfavorable change in product mix. The unfavorable product mix, which includes the unfavorable impact of the reclassification of Viagra IH to EH in 2018, is partially offset by an increase in alliance revenues, which have no associated cost of sales.
- The increase in *Cost of sales* of 5% was primarily driven by an increase in sales volumes for various key products within our product portfolio, and an increase in royalty expenses based on the mix of products sold, partially offset by the favorable impact of foreign exchange.
- The increase in *Selling, informational and administrative expenses* of 8% was primarily driven by additional investment across several of our key products, primarily Xeljanz, Eucrisa, Ibrance, Prevnar 13/Prevenar 13 (pediatric indication) and Eliquis, partially offset by lower healthcare reform expenses as a result of a true up of a prior year amount and decreased investment in Enbrel due to loss of exclusivity across developed Europe.
- The increase in *Research and development expenses* of 11% primarily reflects:
  - increased costs associated with our Phase 3 clinical trials related to our JAK1 inhibitor (which was initiated in December 2017) and the *C. difficile* vaccine program (which was initiated in March 2017);
  - increased costs across the Oncology portfolio, including costs associated with Bavencio studies; and
  - increased costs for our rare disease portfolio,

  partially offset by:
  - lower costs due to the completion of certain clinical studies, including tanezumab and Lyrica.
- The favorable change in *Other (income)/deductions—net* primarily reflects:
  - a $188 million increase in income from collaborations, out-licensing arrangements and sales of compound/product rights;
  - a $45 million increase in Xtandi royalty income; and
  - a $14 million increase in dividend income from our investment in ViiV.

Essential Health Operating Segment

Revenues

EH *Revenues* decrease d $542 million , or 3% , to $15.1 billion , reflecting an operational decrease of $894 million , or 6% , partially offset by the favorable impact of foreign exchange of $352 million , or 2% .

The following provides an analysis of the decrease in EH worldwide *Revenues* :

(MILLIONS OF DOLLARS)		
EH *Revenues* , for the nine months ended October 1, 2017	$	15,639
Operational growth/(decline):		
Decline from the Peri-LOE Products portfolio, driven by lower revenues in developed markets (excluding Viagra EH), primarily due to expected declines in Lyrica in developed Europe and Pristiq in the U.S. due to generic competition		(463)
Decline from the SIP portfolio, driven by lower revenues in developed markets, primarily due to continued legacy Hospira product shortages in the U.S.		(419)
Decline in the LEP portfolio primarily driven by lower revenues in developed markets		(314)
Impact on financial results for the sale of HIS in February 2017. The first nine months of 2018 do not reflect any contribution from HIS global operations, compared to approximately one month of HIS domestic operations and approximately two months of HIS international operations in the same period in 2017		(97)
Positive impact of Viagra, mostly driven by the shift in the reporting of U.S. and Canada Viagra revenues from IH to EH at the beginning of 2018 (due to the loss of exclusivity of Viagra in the U.S. in December 2017), partially offset by lower revenues in developed Europe markets (previously reported in EH)		216
Growth from Biosimilars, primarily from Inflectra in certain channels in the U.S., as well as in developed Europe		165
Other operational factors, net		19
Operational decline, net		(894)
Favorable impact of foreign exchange		352
EH *Revenues* decrease		(542)
EH *Revenues* , for the nine months ended September 30, 2018	$	15,097

Total EH revenues from emerging markets increase d $680 million , or 13% , to $5.8 billion from $5.1 billion , primarily driven by 11% operational growth from the LEP portfolio and 13% operational growth from the SIP portfolio, partially offset by a 2% operational decline from the Peri-LOE Products portfolio. Foreign exchange had a favorable impact of 2% on total EH revenues from emerging markets.

Costs and Expenses

The changes in EH expenses below reflect, among other things, the favorable impact of the February 2017 sale of HIS. The operating results of HIS are included in EH's operating results through February 2, 2017 and, therefore, operating results for EH for the first nine months of 2017 include approximately one month of HIS domestic operations and approximately two months of HIS international operations. Operating results for EH for the first nine months of 2018 do not reflect any contribution from HIS global operations.

- *Cost of sales* as a percentage of *Revenues* increase d 1.8 percentage points, primarily due to:
  - higher sales volume of Inflectra in the U.S. and developed Europe, and higher Pfizer CentreOne sales volumes, both of which carry higher product costs;
  - lower sales volumes and margins as a result of product losses of exclusivity and generic competition in developed markets; and
  - the unfavorable impact of foreign exchange,

  partially offset by:
  - lower sales volumes in the SIP portfolio, which carries a higher cost to produce, in developed markets, primarily due to continued legacy Hospira product shortages in the U.S.; and
  - the non-recurrence of charges related to a product recall that occurred in 2017.
- The increase in *Cost of sales* of 3% was primarily due to:
  - higher sales volumes of Inflectra in the U.S. and developed Europe, and higher Pfizer CentreOne sales volumes, both of which carry higher product costs; and
  - the unfavorable impact of foreign exchange,

  partially offset by:
  - lower sales volumes driven by product losses of exclusivity and generic competition in developed markets; and
  - the non-recurrence of charges related to a product recall that occurred in 2017.

- *Selling, informational and administrative expenses* decrease d 9% mainly due to lower advertising, promotional and field force expenses, reflecting the benefits of cost-reduction and productivity initiatives, and lower general and administrative expenses, partially offset by additional investments in China and the unfavorable impact of foreign exchange.
- *Research and development expenses* decrease d 10% , primarily due to decreased spending for biosimilars as several programs have reached completion.
- The unfavorable change in *Other (income)/deductions—net* primarily reflects the non-recurrence of income from resolution of a contract disagreement, the non-recurrence of a gain on the redemption of an acquired bond in 2017 and the unfavorable impact of foreign exchange, partially offset by an increase in income from collaborations, out-licensing arrangements and sales of compound/product rights.

ANALYSIS OF THE CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME

Changes in the components of *Accumulated other comprehensive loss* for the third quarter and first nine months of 2018 reflect the following:

- For *Foreign currency translation adjustments, net ,* the third quarter of 2018 primarily reflects the strengthening of the U.S. dollar against the Chinese renminbi, U.K. pound and Australian dollar, and for the first nine months of 2018 , primarily reflects the strengthening of the U.S. dollar against the U.K. pound, Turkish lira and Brazilian real, partially offset by the weakening of the U.S. dollar against the Japanese yen.
- For *Unrealized holding gains/(losses) on derivative financial instruments, net* and *Unrealized holding gains/(losses) on available-for-sale securities, net ,* reflects the impact of fair value re-measurements and the reclassification of amounts into income. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 1B. Basis of Presentation and Significant Accounting Policies—Adoption of New Accounting Standards* and Notes to Condensed Consolidated Financial Statements— *Note 7. Financial Instruments* .
- For *Benefit plans: actuarial gains/(losses), net ,* the third quarter of 2018 primarily reflects (i) the amortization of changes in the pension benefit obligation previously recognized in *Other comprehensive income,* (ii) the favorable impact of foreign exchange, (iii) settlement activity and (iv) an $8 million reduction in the plan liability due to an interim re-measurement. For the first nine months of 2018 , primarily reflects (i) the amortization of changes in the pension benefit obligation previously recognized in *Other comprehensive income* , (ii) a $92 million reduction in the plan liability due to an interim re-measurement, (iii) settlement activity and (iv) the favorable impact of foreign exchange. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 10. Pension and Postretirement Benefit Plans* .
- For *Benefit plans: prior service costs and other, net* , the third quarter and the first nine months of 2018 reflect the reclassification into income of amounts related to (i) amortization of changes in prior service costs and credits previously recognized in *Other comprehensive income* and (ii) curtailment activity. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 10. Pension and Postretirement Benefit Plans* .
- For *Tax provision/(benefit) on other comprehensive income/(loss) ,* the first nine months of 2018 reflect the reclassification of the stranded tax amounts related to the TCJA from AOCI to *Retained earnings,* which was recorded in the first quarter of 2018. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 1B. Basis of Presentation and Significant Accounting Policies—Adoption of New Accounting Standards* and Notes to Condensed Consolidated Financial Statements— *Note 5D. Tax Matters : Tax Provision/(Benefit) on Other Comprehensive Income/(Loss)* .

ANALYSIS OF THE CONDENSED CONSOLIDATED BALANCE SHEETS

For information about certain of our financial assets and liabilities, including *Cash and cash equivalents, Short-term investments, Long-term investments, Short-term borrowings, including current portion of long-term debt* , and *Long-term debt* , see the “Analysis of the Condensed Consolidated Statements of Cash Flows” section of this MD&A, the “Analysis of Financial Condition, Liquidity and Capital Resources: Selected Measures of Liquidity and Capital Resources” section of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 7. Financial Instruments* .

For information about events and circumstances impacting our tax-related accounts, see Notes to Condensed Consolidated Financial Statements— *Note 5. Tax Matters* .

For information related to changes in *Accumulated other comprehensive loss* , see the “Analysis of the Condensed Consolidated Statements of Comprehensive Income” section of this MD&A and Notes to Condensed Consolidated Financial Statements— *Note 6. Accumulated Other Comprehensive Loss, Excluding Noncontrolling Interests* .

The changes in our asset and liability accounts as of September 30, 2018 , compared to December 31, 2017 , generally reflect, among other things, fluctuations in foreign currency exchange rates, as well as the impact of the adoption of new accounting standards in the first quarter of 2018 . The following explanations exclude the impact of foreign exchange and the impact of the adoption of new accounting standards in the first quarter of 2018 (see Notes to Condensed Consolidated Financial Statements—

Note 1B. Basis of Presentation and Significant Accounting Policies : Adoption of New Accounting Standards for additional information).

- For *Trade accounts receivable, less allowance for doubtful accounts,* the change reflects the timing of sales and collections in the normal course of business.
- For *Inventories,* the change reflects the increases for certain products to meet targeted levels in the normal course of business, including inventory build for supply recovery, network strategy and new product launches.
- For *Other current assets,* the change reflects an increase in receivables associated with derivative financial instruments, partially offset by the receipt of a milestone payment related to the first marketing authorization for ertugliflozin (see Notes to Condensed Consolidated Financial Statements— *Note 2D. Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment : Collaborative Arrangements*).
- For *PP&E* , the change primarily reflects capital additions in the normal course of business, partially offset by depreciation during the period.
- For *Identifiable intangible assets, less accumulated amortization* , the change primarily reflects amortization for the period, partially offset by an intangible asset recorded in connection with the EU approval of Mylotarg (see Notes to Condensed Consolidated Financial Statements— *Note 9A. Identifiable Intangible Assets and Goodwill : Identifiable Intangible Assets).*
- For *Trade accounts payable,* the change reflects the timing of purchases and payments in the normal course of business.
- For *Other current liabilities* , the change reflects a decrease in liabilities associated with:
  - payments for contingent consideration obligations;
  - payments to settle certain legal and product liability obligations;
  - payments for restructuring activities;
  - payments for the current portion of obligations recorded in connection with the U.S. approval of Bosulif, and the EU and U.S. approvals of Besponsa (see Notes to Condensed Consolidated Financial Statements— *Note 7E. Financial Instruments : Other Noncurrent Liabilities)* ; and
  - payables related to derivative financial instruments,

  partially offset by increases related to:
  - payments and accruals in the normal course of business; and
  - reclassifications from noncurrent liabilities.
- For *Pension benefit obligations, net* , the decrease primarily reflects a voluntary pension contribution, direct employer benefit payments, and an interim re-measurement in a U.S. non-qualified plan.
- For *Other noncurrent liabilities* , the change reflects an increase in liabilities associated with:
  - an increase in payables, associated with derivative financial instruments;
  - an increase in liabilities associated with the sale-leaseback of our New York headquarters (see Notes to Condensed Consolidated Financial Statements— *Note 12C. Contingencies and Certain Commitments: Certain Commitments* for additional information); and
  - a change in the fair value of contingent consideration (see Notes to Condensed Consolidated Financial Statements— *Note 4 . Other (Income)/Deductions—Net*),

  partially offset by:
  - reclassifications to current liabilities.
- For *Treasury stock,* the change reflects $4.0 billion paid to Citibank in March 2018 pursuant to the terms of an accelerated share repurchase agreement as well as open market share repurchases. See Notes to Condensed Consolidated Financial Statements— *Note 12C. Contingencies and Certain Commitments : Certain Commitments* for additional information.

ANALYSIS OF THE CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS

(MILLIONS OF DOLLARS)	Nine Months Ended September 30, 2018	Nine Months Ended October 1, 2017	% Change
Cash provided by/(used in):			
Operating activities	$ 11,089	$ 9,713	14
Investing activities	5,289	19	*
Financing activities	(14,034)	(9,607)	46
Effect of exchange-rate changes on cash and cash equivalents and restricted cash and cash equivalents	(116)	67	*
Net increase in *Cash and cash equivalents* and restricted cash and cash equivalents	$ 2,227	$ 193	*

* Calculation not meaningful or results are equal to or greater than 100%.

In the condensed consolidated statements of cash flows, the line item *Other changes in assets and liabilities, net of acquisitions and divestitures* is presented excluding the effects of changes in foreign currency exchange rates, as these changes do not reflect actual cash inflows or outflows, and excluding any other significant non-cash movements. Accordingly, the amounts shown will not necessarily agree with the changes in the assets and liabilities that are presented in our condensed consolidated balance sheets.

Operating Activities

Our net cash provided by operating activities was $11.1 billion in the first nine months of 2018 , compared to $9.7 billion in the same period in 2017 . The increase in net cash provided by operating activities reflects an increase in net cash generated from net income. The net cash generated reflects the timing of receipts from customers and payments to vendors in the ordinary course of business.

In the first nine months of 2018 , the change in the line item *Other adjustments, net* primarily reflects, among other items:

- unrealized net gains on equity securities resulting from the adoption of a new accounting standard on January 1, 2018 related to financial assets and liabilities (see Notes to Condensed Consolidated Financial Statements— *Note 1B. Basis of Presentation and Significant Accounting Policies: Adoption of New Accounting Standards*);
- a non-cash gain associated with our transaction with Bain Capital to create a new biopharmaceutical company to continue development of a portfolio of clinical and preclinical stage neuroscience assets (see Notes to Condensed Consolidated Financial Statements— *Note 2B. Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment : Divestitures*); and
- a non-cash gain on the contribution of Pfizer's allogeneic CAR T developmental program assets, in connection with our contribution agreement with Allogene (see Notes to Condensed Consolidated Financial Statements— *Note 2B. Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment : Divestitures*),

partially offset by:

- net losses on foreign exchange contracts hedging a portion of our forecasted intercompany inventory sales (that fixes the cost of inventory sold later to customers); and
- a decrease in gains on the sale of property, plant and equipment.

In the first nine months of 2018 and 2017 , the line item *Other changes in assets and liabilities, net of acquisitions and divestitures,* primarily reflects changes, in the normal course of business, in trade accounts receivable, inventories, other current assets, other noncurrent assets, trade accounts payable, accrued compensation and other current and noncurrent liabilities.

For additional information about changes in other assets and liabilities account balances, see the "Analysis of the Condensed Consolidated Balance Sheets" in this MD&A.

Investing Activities

Our net cash provided by investing activities was $5.3 billion in the first nine months of 2018 , compared to net cash provided by investing activities of $19 million in the same period in 2017 . The increase in net cash provided by investing activities was primarily attributable to:

- an increase in net proceeds generated from the sale of investments of $4.5 billion in 2018 for cash needs; and
- a decrease in cash used for acquisitions, net of cash acquired of $1.0 billion due to the acquisition of the development and commercialization rights to AstraZeneca's small molecule anti-infectives business and substantially all of the remaining consideration for the Medivation acquisition in 2017 (see Notes to Condensed Consolidated Financial Statements— *Note 2A*.

Acquisition, Divestitures, Licensing Arrangements, Collaborative Arrangements and Privately Held Investment : Acquisition).

Financing Activities

Our net cash used in financing activities was $14.0 billion in the first nine months of 2018 , compared to $9.6 billion in the same period in 2017 . The increase in net cash used in financing activities was primarily attributable to:

- $3.2 billion less proceeds raised from short-term borrowings in the first nine months of 2018 , compared to the first nine months of 2017 ; and
- higher purchases of common stock of $2.2 billion ,

partially offset by:

- lower repayments on long-term debt of $1.4 billion .

ANALYSIS OF FINANCIAL CONDITION, LIQUIDITY AND CAPITAL RESOURCES

We rely largely on operating cash flows, short-term investments, short-term commercial paper borrowings and long-term debt to provide for our liquidity requirements. We continue our efforts to improve cash inflows through working capital efficiencies. We target specific areas of focus including accounts receivable, inventories, accounts payable, and other working capital, which allows us to optimize our operating cash flows. Due to our significant operating cash flows as well as our financial assets, access to capital markets and available lines of credit and revolving credit agreements, we believe that we have, and will maintain, the ability to meet our liquidity needs for the foreseeable future, which include:

- the working capital requirements of our operations, including our R&D activities;
- investments in our business;
- dividend payments and potential increases in the dividend rate;
- share repurchases;
- the cash requirements associated with our cost-reduction/productivity initiatives;
- paying down outstanding debt;
- contributions to our pension and postretirement plans; and
- business-development activities.

Our long-term debt is rated high-quality by both S&P and Moody's. See the "Credit Ratings" section below. As market conditions change, we continue to monitor our liquidity position. We have taken and will continue to take a conservative approach to our financial investments. Both short-term and long-term investments consist primarily of high-quality, highly liquid, well-diversified available-for-sale debt securities.

Selected Measures of Liquidity and Capital Resources

The following table provides certain relevant measures of our liquidity and capital resources:

(MILLIONS OF DOLLARS, EXCEPT RATIOS AND PER COMMON SHARE DATA)	September 30, 2018	December 31, 2017
Selected financial assets:		
Cash and cash equivalents [(a)]	$ 3,559	$ 1,342
Short-term investments [(a)]	13,680	18,650
Long-term investments [(a)]	6,444	7,015
	23,684	27,007
Debt:		
Short-term borrowings, including current portion of long-term debt	7,385	9,953
Long-term debt	33,652	33,538
	41,037	43,491
Selected net financial liabilities [(b)]	$ (17,353)	$ (16,484)
Working capital [(c)]	$ 12,569	$ 10,714
Ratio of current assets to current liabilities	1.43:1	1.35:1
Total Pfizer Inc. shareholders' equity per common share [(d)]	$ 12.21	$ 11.93

[(a)] See Notes to Condensed Consolidated Financial Statements— *Note 7. Financial Instruments* for a description of certain assets held and for a description of credit risk related to our financial instruments held.

[(b)] The increase in selected net financial liabilities was primarily driven by the decrease in short-term investments used for cash needs, partially offset by the repayment of debt. We retain a strong financial liquidity position as a result of our net cash provided by operating activities, our high-quality

financial asset portfolio and access to capital markets. Both Moody's and S&P rating agencies maintained our strong investment-grade corporate debt rating subsequent to the acquisitions of Medivation and Anacor. For additional information, see the "Credit Ratings" section of this MD&A.

(c) The increase in working capital was primarily due to:

- the timing of accruals, cash receipts and payments in the ordinary course of business;
- a decrease in short-term borrowings as a result of repayments of commercial paper; and
- an increase in inventory related to increases for certain products to meet targeted levels in the normal course of business, including inventory build for supply recovery, network strategy and new product launches,

partially offset by:

- a decrease in S *hort-term investments* mainly driven by the financing requirements for share repurchase activities, dividend payments, capital expenditures and debt repayment, partially offset by operating cash flow generation, cash from employee stock option exercises and reclassification of long-term to short-term investments;
- an increase in income taxes payable related to the timing of accruals in certain major markets in the ordinary course of business and the reclassification of the first federal installment of transition tax previously recorded in noncurrent liabilities; and
- the net impact of foreign currency exchange.

(d) Represents total Pfizer Inc. shareholders' equity divided by the actual number of common shares outstanding (which excludes treasury stock).

On September 7, 2018, we completed a public offering of $5.0 billion aggregate principal amount of senior unsecured notes (see *Notes to Consolidated Financial Statements—Note 7D. Financial Instruments : Long-Term Debt)* .

On October 6, 2016, we announced that we entered into a definitive agreement under which ICU Medical agreed to acquire all of our global infusion systems net assets, HIS. The revised transaction closed on February 3, 2017. At closing, we received 3.2 million newly issued shares of ICU Medical common stock (as originally agreed). In August 2018, we sold 700,000 shares of ICU Medical common stock. We continue to hold 2.5 million shares of ICU Medical common stock. The lock-up period under the shareholder agreement that we entered into with ICU Medical in connection with these shares expired on August 3, 2018 and the shares are registrable upon our request subject to the terms thereof. Given that the shares were received in connection with our divestiture of the HIS business, and that our business model is generally not to invest in equities, we are evaluating our options to monetize the shares subject to market conditions and other relevant factors.

For additional information about the sources and uses of our funds, see the "Analysis of the Condensed Consolidated Balance Sheets" and the "Analysis of the Condensed Consolidated Statements of Cash Flows" sections of this MD&A.

Domestic and International Selected Financial Assets

Many of our operations are conducted outside the U.S., and significant portions of our selected financial assets are held internationally. The amount of funds held in U.S. tax jurisdictions can fluctuate due to the timing of receipts and payments in the ordinary course of business and due to other reasons, such as business-development activities. As part of our ongoing liquidity assessments, we regularly monitor the mix of domestic and international cash flows (both inflows and outflows). Given the recent changes in tax law under the TCJA, which includes transitioning U.S. international taxation from a worldwide tax system to a territorial tax system, in the fourth quarter of 2017, we recorded an estimated repatriation tax on deemed repatriated accumulated post-1986 earnings of foreign subsidiaries for which we plan to elect payment over eight years through 2026. These changes will also allow us to more easily access our selected financial assets globally. As a result of the enactment of the TCJA, in 2018 we repatriated the majority of our cash we held internationally as of year-end 2017.

Credit Ratings

Two major corporate debt-rating organizations, Moody's and S&P, assign ratings to our short-term and long-term debt. A security rating is not a recommendation to buy, sell or hold securities and the rating is subject to revision or withdrawal at any time by the rating organization. Each rating should be evaluated independently of any other rating.

The following table provides the current ratings assigned by these rating agencies to our commercial paper and senior unsecured long-term debt:

	Pfizer Commercial Paper	Pfizer Long-Term Debt	
NAME OF RATING AGENCY	Rating	Rating	Date of Last Rating Change
Moody's [a]	P-1	A1	October 2009
S&P [b]	A-1+	AA	October 2009

(a) In September 2016, Moody's updated their credit outlook from negative outlook to stable.

(b) In April 2016, S&P updated their credit outlook from negative watch to stable.

Debt Capacity—Lines of Credit

We have available lines of credit and revolving credit agreements with a group of banks and other financial intermediaries. We typically maintain cash and cash equivalent balances and short-term investments in excess of our commercial paper and other short-term borrowings. As of September 30, 2018 , we had access to $7.6 billion of lines of credit, of which $571 million expire within one year. Of these lines of credit, $7.6 billion were unused, of which our lenders have committed to loan us $7.1 billion at our request, primarily under our revolving credit facility expiring in 2022, and may be used to support our commercial paper borrowings.

Global Economic Conditions—General

The global economic environment has not had, nor do we anticipate it will have, a material impact on our liquidity or capital resources. Due to our significant operating cash flows, financial assets, access to capital markets and available lines of credit and revolving credit agreements, we continue to believe that we have, and will maintain, the ability to meet our liquidity needs for the foreseeable future. We monitor our liquidity position continuously in the face of evolving economic conditions. For additional information see “Overview of Our Performance, Operating Environment, Strategy and Outlook—Our Operating Environment—The Global Economic Environment” section in this MD&A.

Global Economic Conditions—Venezuela Operations

Our Venezuela operations continue to operate with the U.S. dollar as the functional currency due to the hyperinflationary status of the Venezuelan economy.

We used the Venezuelan bolivar soberano rate of 60.27 as our best estimate to revalue our Venezuelan bolivar denominated net monetary assets. The current DICOM rate is about 64.89 . Future actions by the Venezuelan government in response to economic uncertainties could impact the recoverability of our investment in Venezuela, which could result in an impairment charge and, under extreme circumstances, could impact our ability to continue to operate in the country in the same manner as we have historically. We have in Venezuela a few net monetary assets and $46 million of non-monetary assets, and $11 million of deferred foreign exchange losses reported in the balance sheet in *Accumulated other comprehensive loss—Foreign currency translation adjustments* at August 26, 2018 , our international quarter-end.

Global Economic Conditions—Argentina Operations

Our Argentina operations function in a hyperinflationary economy. The impact to Pfizer is not considered material.

Off-Balance Sheet Arrangements

In the ordinary course of business and in connection with the sale of assets and businesses and other transactions, we often indemnify our counterparties against certain liabilities that may arise in connection with a transaction or that are related to events and activities prior to or following a transaction. If the indemnified party were to make a successful claim pursuant to the terms of the indemnification, we may be required to reimburse the loss. These indemnification obligations generally are subject to various restrictions and limitations. Historically, we have not paid significant amounts under these provisions and, as of September 30, 2018 , the estimated fair value of our indemnity obligations was not significant.

Certain of our co-promotion or license agreements give our licensors or partners the rights to negotiate for, or in some cases to obtain under certain financial conditions, co-promotion or other rights in specified countries with respect to certain of our products.

Share-Purchase Plans and Accelerated Share Repurchase Agreements

Our December 2015 $11 billion share repurchase program was exhausted in the third quarter of 2018.

In December 2017, the Board of Directors authorized an additional $10 billion share repurchase program, and share repurchases commenced thereunder in the third quarter of 2018 (the 2017 program).

On March 12, 2018 , we entered into an accelerated share repurchase agreement with Citibank to repurchase $4.0 billion of our common stock. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 12 . Contingencies and Certain Commitments* and “Unregistered Sales of Equity Securities and Use of Proceeds—Issuer Purchases of Equity Securities” in Part II, Item 2 of this Quarterly Report on Form 10-Q.

The following table provides the number of shares of our common stock purchased and the cost of purchases under our publicly announced share purchase plans, including our accelerated share repurchase agreements:

	Three Months Ended		Nine Months Ended	
(SHARES IN MILLIONS, DOLLARS IN BILLIONS)	September 30, 2018 [a]	October 1, 2017	September 30, 2018 [a]	October 1, 2017 [b]
Shares of common stock purchased	47	—	192	150
Cost of purchase	$ 1.1	$ —	$ 7.2	$ 5.0

[a] Represents shares purchased pursuant to an accelerated share repurchase agreement with Citibank entered into on March 12, 2018, as well as other share repurchases. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 12 . Contingencies and Certain Commitments* and "Unregistered Sales of Equity Securities and Use of Proceeds—Issuer Purchases of Equity Securities" in Part II, Item 2 of this Quarterly Report on Form 10-Q and the Quarterly Report on Form 10-Q for the quarterly period ended April 1, 2018.

[b] Represents shares purchased pursuant to an accelerated share repurchase agreement entered into on February 2, 2017. For additional information, see Notes to Consolidated Financial Statements— *Note 12 . Equity* in our 2017 Financial Report.

At September 30, 2018 , our remaining share-purchase authorization under the 2017 program was approximately $9.2 billion .

Dividends on Common Stock

In September 2018, our Board of Directors declared a dividend of $0.34 per share, payable on December 3, 2018 , to shareholders of record at the close of business on November 9, 2018 .

NEW ACCOUNTING STANDARDS

Recently Adopted Accounting Standards

See Notes to Condensed Consolidated Financial Statements— *Note 1B. Basis of Presentation and Significant Accounting Policies: Adoption of New Accounting Standards.*

Recently Issued Accounting Standards, Not Adopted as of September 30, 2018

Standard/Description	Effective Date	Effect on the Financial Statements or Other Significant Matters
In February 2016, the FASB issued new guidance on accounting for **leases** . The new ASU provides guidance for both lessee and lessor accounting models. Among other things, the new guidance requires that a right of use asset and a lease liability be recognized for leases with a duration of greater than one year. Since its issuance, the FASB has issued several ASUs, including amending the guidance to offer an additional transition method.	January 1, 2019. Earlier application is permitted.	We have made substantial progress in completing our review of the impact of this new guidance. We anticipate recognition of approximately $2 billion of additional assets and corresponding liabilities on our balance sheet. We have also assessed the potential impact of embedded leases on our consolidated financial statements, given our manufacturing outsourcing, service arrangements and other agreements. In connection with this guidance we are currently designing new global processes and technological solutions to provide the appropriate financial accounting and disclosure data. We continue to monitor changes, modifications, clarifications or interpretations undertaken by the FASB, which may impact our conclusions.
In March 2017, the FASB issued new guidance that shortens the **amortization period for certain callable debt securities held at a premium** . The new guidance requires the premium to be amortized to the earliest call date.	January 1, 2019. Early application is permitted, including in interim periods, so long as any adjustments are reflected as of the beginning of the fiscal year that includes the interim period in which the guidance is applied.	We do not have any investments with features subject to this standard and do not expect this new guidance to have a material impact on our consolidated financial statements.
In July 2017, the FASB issued new guidance on accounting for **certain financial instruments with characteristics of liabilities and equity,** and accounting for certain financial instruments with **down round features** (a feature in a financial instrument that reduces the strike price of an issued financial instrument if the issuer sells shares of its stock for an amount less than the currently stated strike price of the issued financial instrument or issues an equity-linked financial instrument with a strike price below the currently stated strike price of the issued financial instrument).	January 1, 2019. Earlier application is permitted.	We do not have any financial instruments with features subject to this standard and do not expect this new guidance to have a material impact on our consolidated financial statements.
In June 2018, the FASB issued new guidance to simplify the accounting for **share-based payments to nonemployees** by aligning it with the accounting for share-based payments to employees, with certain exceptions. Under the guidance, the measurement of equity-classified nonemployee awards will be fixed at the grant date.	January 1, 2019. Early adoption is permitted, including in interim periods.	We do not have any share-based awards issued to nonemployees and do not expect this new guidance to have a material impact on our consolidated financial statements.

Standard/Description	Effective Date	Effect on the Financial Statements or Other Significant Matters
In June 2016, the FASB issued new guidance on accounting for **credit losses of financial instruments** . The new guidance replaces the probable initial recognition threshold for incurred loss estimates in current GAAP with a methodology that reflects expected credit loss estimates.	January 1, 2020. Earlier application is permitted as of fiscal years beginning after December 15, 2018, including interim periods within that fiscal year.	We are assessing the impact of the provisions of this new guidance on our consolidated financial statements. This standard includes our financial instruments, such as accounts receivable, and investments that are generally of high credit quality. Previously, when credit losses were measured under GAAP, an entity generally only considered past events and current conditions in measuring the incurred loss. The new guidance requires us to identify, analyze, document and support new methodologies for quantifying expected credit loss estimates for our financial instruments, using information such as historical experience and current economic environmental conditions, plus the use of reasonable supportable forecast information.
In January 2017, the FASB issued new guidance for **goodwill impairment testing** . The new guidance eliminates the requirement to perform a hypothetical purchase price allocation to measure goodwill impairment. Under the new guidance the goodwill impairment test is performed by comparing the fair value of a reporting unit with its carrying amount, and recognizing an impairment charge for the amount by which the carrying amount of the reporting unit exceeds its fair value, although it cannot exceed the total amount of goodwill allocated to that reporting unit.	January 1, 2020. Earlier application is permitted.	We do not expect this new guidance to have a material impact on our consolidated financial statements.
In August 2018, the FASB issued new guidance related to **customers' accounting for implementation costs incurred in a cloud computing arrangement that is considered a service contract** . The new guidance aligns the requirements for capitalizing implementation costs in such arrangements with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software. The new guidance can be adopted either prospectively or retrospectively.	January 1, 2020. Earlier application is permitted.	We are assessing the impact of the provisions of this new guidance on our consolidated financial statements.
In November 2018, the FASB issued new guidance clarifying the interaction between the accounting guidance for **collaboration agreements** and **revenue from contracts with customers** .	January 1, 2020. Earlier application is permitted	We are assessing the impact of the provisions of this new guidance on our consolidated financial statements.

FORWARD-LOOKING INFORMATION AND FACTORS THAT MAY AFFECT FUTURE RESULTS

This report and other written or oral statements that we make from time to time contain forward-looking statements. Such forward-looking statements involve substantial risks and uncertainties. We have tried, wherever possible, to identify such statements by using words such as "will," "may," "could," "likely," "ongoing," "anticipate," "estimate," "expect," "project," "intend," "plan," "believe," "assume," "target," "forecast," "guidance," "goal," "objective," "aim" and other words and terms of similar meaning or by using future dates in connection with any discussion of, among other things, our anticipated operating and financial performance, business plans and prospects, in-line products and product candidates, including anticipated regulatory submissions, data read-outs, study starts, approvals, performance, timing of exclusivity and potential benefits of Pfizer's products and product candidates, strategic reviews, capital allocation, business-development plans, the benefits expected from our plans to organize our commercial operations into three businesses effective at the beginning of the company's 2019 fiscal year, our acquisitions and other business development activities, our ability to successfully capitalize on growth opportunities, manufacturing and product supply and plans relating to share repurchases and dividends. In particular, these include statements relating to future actions, business plans and prospects, our acquisitions and other business development activities, the disposition of the HIS net assets, prospective products or product approvals, future performance or results of current and anticipated products, sales efforts, expenses, interest rates, foreign exchange rates, the outcome of contingencies, such as legal proceedings, plans relating to share repurchases and dividends, government regulation and financial results, including, in particular, the anticipated progress in remediation efforts at certain of our Hospira manufacturing facilities set forth in the "Overview of Our Performance, Operating Environment, Strategy and Outlook—Our Business—Product Manufacturing" section of this MD&A, our plans to organize our company into three businesses effective at the beginning of our 2019 fiscal year and our expectations regarding growth set forth in the "Overview of Our Performance, Operating Environment, Strategy and Outlook—Our Strategy—Organizing for Growth" section of this MD&A, the anticipated timeframe for any decision regarding strategic alternatives for Pfizer Consumer Healthcare set forth in the "Overview of Our Performance, Operating Environment, Strategy and Outlook—Our Business" and "—Our Strategy—Our Business Development Initiatives" sections of this MD&A, our anticipated liquidity position set forth in the "Overview of Our Performance, Operating Environment, Strategy and Outlook—The Global Economic Environment" and the "Analysis of Financial Condition, Liquidity and Capital Resources" sections of this MD&A, the financial guidance set forth in the "Our Financial Guidance for 2018 " section of this MD&A, the anticipated costs and cost savings, including from our acquisition of Hospira and our cost-reduction/productivity initiatives set forth in the "Costs and Expenses—Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives" section of this MD&A and in Notes to Condensed Consolidated Financial Statements— *Note 3. Restructuring Charges and Other Costs Associated with Acquisitions and Cost-Reduction/Productivity Initiatives ,* the benefits expected from our business development transactions and the contributions that we expect to make from our general assets to our pension and postretirement plans during 2018 set forth in Notes to Condensed Consolidated Financial Statements— *Note 10. Pension and Postretirement Benefit Plans* . Among the factors that could cause actual results to differ materially from past results and future plans and projected future results are the following:

- the outcome of research and development activities including, without limitation, the ability to meet anticipated pre-clinical and clinical trial commencement and completion dates, regulatory submission and approval dates, and launch dates for product candidates, as well as the possibility of unfavorable pre-clinical and clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data;
- decisions by regulatory authorities regarding whether and when to approve our drug applications, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling, ingredients and other matters that could affect the availability or commercial potential of our products; uncertainties regarding our ability to address the comments received by us from regulatory authorities such as the FDA and the EMA with respect to certain of our drug applications to the satisfaction of those authorities; and recommendations by technical or advisory committees, such as ACIP, that may impact the use of our vaccines;
- the speed with which regulatory authorizations, pricing approvals and product launches may be achieved;
- the outcome of post-approval clinical trials, which could result in the loss of marketing approval for a product or changes in the labeling for, and/or increased or new concerns about the safety or efficacy of, a product that could affect its availability or commercial potential;

- risks associated with preliminary, early stage or interim data, including the risk that final results of studies for which preliminary, early stage or interim data have been provided and/or additional clinical trials may be different from (including less favorable than) the preliminary, early stage or interim data results and may not support further clinical development of the applicable product candidate or indication;
- the success of external business-development activities, including the ability to identify and execute on potential business development opportunities, the ability to satisfy the conditions to closing of announced transactions in the anticipated time frame or at all, the ability to realize the anticipated benefits of any such transactions, and the potential need to obtain additional equity or debt financing to pursue these opportunities which could result in increased leverage and impact our credit ratings;
- competitive developments, including the impact on our competitive position of new product entrants, in-line branded products, generic products, private label products, biosimilars and product candidates that treat diseases and conditions similar to those treated by our in-line drugs and drug candidates;
- the implementation by the FDA and regulatory authorities in certain other countries of an abbreviated legal pathway to approve biosimilar products, which could subject our biologic products to competition from biosimilar products, with attendant competitive pressures, after the expiration of any applicable exclusivity period and patent rights;
- risks related to our ability to develop and launch biosimilars, including risks associated with “at risk” launches, defined as the marketing of a product by Pfizer before the final resolution of litigation (including any appeals) brought by a third party alleging that such marketing would infringe one or more patents owned or controlled by the third party, and access challenges for our biosimilar products where our product may not receive appropriate formulary access or remains in a disadvantaged position relative to the innovator product;
- the ability to meet competition from generic, branded and biosimilar products after the loss or expiration of patent protection for our products or competitor products;
- the ability to successfully market both new and existing products domestically and internationally;
- difficulties or delays in manufacturing, including delays caused by natural events, such as hurricanes; supply shortages at our facilities; and legal or regulatory actions, such as warning letters, suspension of manufacturing, seizure of product, debarment, injunctions or voluntary recall of a product;
- trade buying patterns;
- the impact of existing and future legislation and regulatory provisions on product exclusivity;
- trends toward managed care and healthcare cost containment, and our ability to obtain or maintain timely or adequate pricing or formulary placement for our products;
- the impact of any significant spending reductions or cost controls affecting Medicare, Medicaid or other publicly funded or subsidized health programs or changes in the tax treatment of employer-sponsored health insurance that may be implemented;
- the impact of any U.S. healthcare reform or legislation, including any replacement, repeal, modification or invalidation of some or all of the provisions of the U.S. Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act;
- U.S. federal or state legislation or regulatory action and/or policy efforts affecting, among other things, pharmaceutical product pricing, reimbursement or access, including under Medicaid, Medicare and other publicly funded or subsidized health programs; patient out-of-pocket costs for medicines, manufacturer prices and/or price increases that could result in new mandatory rebates and discounts or other pricing restrictions; the importation of prescription drugs from outside the U.S. at prices that are regulated by governments of various foreign countries; restrictions on direct-to-consumer advertising; limitations on interactions with healthcare professionals; or the use of comparative effectiveness methodologies that could be implemented in a manner that focuses primarily on the cost differences and minimizes the therapeutic differences among pharmaceutical products and restricts access to innovative medicines; as well as pricing pressures for our products as a result of highly competitive insurance markets;
- legislation or regulatory action in markets outside the U.S. affecting pharmaceutical product pricing, reimbursement or access, including, in particular, continued government-mandated reductions in prices and access restrictions for certain biopharmaceutical products to control costs in those markets;
- the exposure of our operations outside the U.S. to possible capital and exchange controls, expropriation and other restrictive government actions, changes in intellectual property legal protections and remedies, as well as political unrest, unstable governments and legal systems and inter-governmental disputes;
- contingencies related to actual or alleged environmental contamination;
- claims and concerns that may arise regarding the safety or efficacy of in-line products and product candidates;

- any significant breakdown, infiltration or interruption of our information technology systems and infrastructure;
- legal defense costs, insurance expenses and settlement costs;
- the risk of an adverse decision or settlement and the adequacy of reserves related to legal proceedings, including patent litigation, such as claims that our patents are invalid and/or do not cover the product of the generic drug manufacturer or where one or more third parties seeks damages and/or injunctive relief to compensate for alleged infringement of its patents by our commercial or other activities, product liability and other product-related litigation, including personal injury, consumer, off-label promotion, securities, antitrust and breach of contract claims, commercial, environmental, government investigations, employment and other legal proceedings, including various means for resolving asbestos litigation, as well as tax issues;
- the risk that our currently pending or future patent applications may not result in issued patents, or be granted on a timely basis, or any patent-term extensions that we seek may not be granted on a timely basis, if at all;
- our ability to protect our patents and other intellectual property, both domestically and internationally;
- interest rate and foreign currency exchange rate fluctuations, including the impact of possible currency devaluations in countries experiencing high inflation rates;
- governmental laws and regulations affecting domestic and foreign operations, including, without limitation, tax obligations and changes affecting the tax treatment by the U.S. of income earned outside the U.S. that may result from pending and possible future proposals, including further clarifications and/or interpretations of the recently passed TCJA;
- any significant issues involving our largest wholesale distributors, which account for a substantial portion of our revenues;
- the possible impact of the increased presence of counterfeit medicines in the pharmaceutical supply chain on our revenues and on patient confidence in the integrity of our medicines;
- the end result of any negotiations between the U.K. government and the EU regarding the terms of the U.K.'s exit from the EU, which could have implications on our research, commercial and general business operations in the U.K. and the EU, including the approval and supply of our products;
- any significant issues that may arise related to the outsourcing of certain operational and staff functions to third parties, including with regard to quality, timeliness and compliance with applicable legal requirements and industry standards;
- any significant issues that may arise related to our joint ventures and other third-party business arrangements;
- changes in U.S. generally accepted accounting principles;
- further clarifications and/or changes in interpretations of existing laws and regulations, or changes in laws and regulations, in the U.S. and other countries;
- uncertainties related to general economic, political, business, industry, regulatory and market conditions including, without limitation, uncertainties related to the impact on us, our customers, suppliers and lenders and counterparties to our foreign-exchange and interest-rate agreements of challenging global economic conditions and recent and possible future changes in global financial markets; the related risk that our allowance for doubtful accounts may not be adequate; and the risks related to volatility of our income due to changes in the market value of equity investments;
- any changes in business, political and economic conditions due to actual or threatened terrorist activity in the U.S. and other parts of the world, and related U.S. military action overseas;
- growth in costs and expenses;
- changes in our product, segment and geographic mix;
- the impact of purchase accounting adjustments, acquisition-related costs, discontinued operations and certain significant items;
- the impact of acquisitions, divestitures, restructurings, internal reorganizations, including our plans to organize our commercial operations into three businesses effective at the beginning of the company's 2019 fiscal year, and cost-reduction and productivity initiatives, each of which requires upfront costs but may fail to yield anticipated benefits and may result in unexpected costs or organizational disruption;
- the impact of product recalls, withdrawals and other unusual items;
- the risk of an impairment charge related to our intangible assets, goodwill or equity-method investments;
- risks related to internal control over financial reporting;

- risks and uncertainties related to our acquisitions of Hospira, Anacor, Medivation and AstraZeneca's small molecule anti-infectives business, including, among other things, the ability to realize the anticipated benefits of those acquisitions, including the possibility that expected accretion related to the acquisitions of Hospira, Anacor and Medivation will not be realized or will not be realized within the expected time frame; the risk that the businesses will not be integrated successfully; disruption from the transactions making it more difficult to maintain business and operational relationships; risks related to our ability to grow revenues for Xtandi; significant transaction costs; and unknown liabilities; and
- risks and uncertainties related to our evaluation of strategic alternatives for our Consumer Healthcare business, including, among other things, the ability to realize the anticipated benefits of any strategic alternatives we may pursue for our Consumer Healthcare business; the potential for disruption to our business and diversion of management's attention from other aspects of our business; the possibility that such strategic alternatives will not be completed on terms that are advantageous to Pfizer; the possibility that we may be unable to realize a higher value for Pfizer Consumer Healthcare through strategic alternatives; and unknown liabilities.

We cannot guarantee that any forward-looking statement will be realized. Achievement of anticipated results is subject to substantial risks, uncertainties and inaccurate assumptions. Should known or unknown risks or uncertainties materialize or should underlying assumptions prove inaccurate, actual results could vary materially from past results and those anticipated, estimated or projected. Investors should bear this in mind as they consider forward-looking statements, and are cautioned not to put undue reliance on forward-looking statements.

We undertake no obligation to publicly update forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law or by the rules and regulations of the SEC. You are advised, however, to consult any further disclosures we make on related subjects.

Our 2017 Form 10-K listed various important factors that could cause actual results to differ materially from past and projected future results. We note these factors for investors as permitted by the Private Securities Litigation Reform Act of 1995. Readers can find them in Part I, Item 1A, of that filing under the heading "Risk Factors." We incorporate that section of that Form 10-K in this filing and investors should refer to it. Reference is also made to Part II, Item 1A, "Risk Factors," of this Quarterly Report on Form 10-Q. You should understand that it is not possible to predict or identify all such factors. Consequently, you should not consider any such list to be a complete set of all potential risks or uncertainties.

The operating segment information provided in this report does not purport to represent the revenues, costs and income from continuing operations before provision for taxes on income that each of our operating segments would have recorded had each segment operated as a standalone company during the periods presented.

This report includes discussion of certain clinical studies relating to various in-line products and/or product candidates. These studies typically are part of a larger body of clinical data relating to such products or product candidates, and the discussion herein should be considered in the context of the larger body of data. In addition, clinical trial data are subject to differing interpretations, and, even when we view data as sufficient to support the safety and/or effectiveness of a product candidate or a new indication for an in-line product, regulatory authorities may not share our views and may require additional data or may deny approval altogether.

Financial Risk Management

Interest Rate Risk

With respect to our investments, we strive to maintain a predominantly floating–rate basis position, but our strategy may change based on prevailing market conditions.

We currently borrow primarily on a long-term, fixed-rate basis. Historically, we strove to borrow primarily on a floating-rate basis; but in recent years we borrowed on a long-term, fixed-rate basis. From time to time, depending on market conditions, we will change the profile of our outstanding debt by entering into derivative financial instruments like interest rate swaps.

Legal Proceedings and Contingencies

Information with respect to legal proceedings and contingencies required by this Item is incorporated herein by reference to Notes to Condensed Consolidated Financial Statements— *Note 12A. Contingencies and Certain Commitments : Legal Proceedings* in Part I, Item 1, of this Quarterly Report on Form 10-Q.

Item 3. Quantitative and Qualitative Disclosures About Market Risk

Information required by this item is incorporated by reference from the discussion under the heading *Financial Risk Management* in our 2017 Financial Report and Part II, Item 1A, "Risk Factors" of this Quarterly Report on Form 10-Q.

Item 4. Controls and Procedures

As of the end of the period covered by this report, we carried out an evaluation, under the supervision and with the participation of our principal executive officer and principal financial officer, of the effectiveness of the design and operation of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act). Based on this evaluation, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures are effective in alerting them in a timely manner to material information required to be disclosed in our periodic reports filed with the SEC.

During our most recent fiscal quarter, there has not been any change in our internal control over financial reporting (as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II - OTHER INFORMATION

Item 1. Legal Proceedings

The information required by this Item is incorporated herein by reference to Notes to Condensed Consolidated Financial Statements— *Note 12A. Contingencies and Certain Commitments : Legal Proceedings* in Part I, Item 1, of this Quarterly Report on Form 10-Q.

Tax Matters

Additional information with respect to tax matters required by this Item is incorporated herein by reference to Notes to Condensed Consolidated Financial Statements— *Note 5C. Tax Matters: Tax Contingencies* in Part I, Item 1, of this Quarterly Report on Form 10-Q.

We account for income tax contingencies using a benefit recognition model. If our initial assessment fails to result in the recognition of a tax benefit, we regularly monitor our position and subsequently recognize the tax benefit: (i) if there are changes in tax law, analogous case law or there is new information that sufficiently raise the likelihood of prevailing on the technical merits of the position to "more likely than not"; (ii) if the statute of limitations expires; or (iii) if there is a completion of an audit resulting in a favorable settlement of that tax year with the appropriate agency. We regularly re-evaluate our tax positions based on the results of audits of federal, state and foreign income tax filings, statute of limitations expirations, changes in tax law or receipt of new information that would either increase or decrease the technical merits of a position relative to the "more-likely-than-not" standard.

Our assessments are based on estimates and assumptions that have been deemed reasonable by management, but our estimates of unrecognized tax benefits and potential tax benefits may not be representative of actual outcomes, and variation from such estimates could materially affect our financial statements in the period of settlement or when the statutes of limitations expire, as we treat these events as discrete items in the period of resolution. Finalizing audits with the relevant taxing authorities can include formal administrative and legal proceedings, and, as a result, it is difficult to estimate the timing and range of possible changes related to our uncertain tax positions, and such changes could be significant.

Item 1A. Risk Factors

The "Our Operating Environment" and "Forward-Looking Information and Factors That May Affect Future Results" sections of the MD&A of this Quarterly Report on Form 10-Q and Part I, Item 1A, "Risk Factors" of our 2017 Form 10-K are incorporated by reference herein. We are including the following risk factor which should be read in conjunction with our description of risk factors in Part I, Item 1A, "Risk Factors" of our 2017 Form 10-K.

MARKET FLUCTUATIONS IN OUR EQUITY INVESTMENTS

In the first quarter of 2018, we adopted a new accounting standard whereby certain equity investments are measured at fair value with changes in fair value now recognized in net income. We expect the adoption of this new accounting standard may increase the volatility of our income in future periods due to changes in the fair value of equity investments. For additional information, see Notes to Condensed Consolidated Financial Statements— *Note 1B . Basis of Presentation and Significant Accounting Policies: Adoption of New Accounting Standards* .

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds

The following table provides certain information with respect to our purchases of shares of the Company's common stock during the third fiscal quarter of 2018 :

Issuer Purchases of Equity Securities [a]

Period	Total Number of Shares Purchased [a][b]	Average Price Paid per Share [a][b]	Total Number of Shares Purchased as Part of Publicly Announced Plan [a]	Approximate Dollar Value of Shares That May Yet Be Purchased Under the Plan [a]
July 2, 2018 through July 29, 2018	7,765	$ 36.43	—	$ 10,292,715,228
July 30, 2018 through August 26, 2018	10,626	$ 40.45	—	$ 10,292,715,228
August 27, 2018 through September 30, 2018	46,671,505	$ 40.36	46,652,993	$ 9,187,715,502
Total	46,689,896	$ 40.36	46,652,993	

[a] Our December 2015 $11 billion share repurchase program was exhausted in the third quarter of 2018. In December 2017, the Board of Directors authorized an additional $10 billion share repurchase program, and share repurchases commenced thereunder in the third quarter of 2018 (the 2017 program). On March 12, 2018 , we entered into an accelerated share repurchase agreement with Citibank to repurchase $4.0 billion of our common stock and on September 5, 2018, the accelerated share repurchase agreement with Citibank was completed. For additional information, see the Notes to Condensed Consolidated Financial Statements —*Note 12. Contingencies and Certain Commitments* . At September 30, 2018 , our remaining share-purchase authorization under the 2017 program was approximately $9.2 billion .

[b] In addition to the amounts purchased under our share repurchase program, including amounts purchased under the accelerated share repurchase agreement with Citibank, these columns represent (i) 32,041 shares of common stock surrendered to the Company to satisfy tax withholding obligations in connection with the vesting of awards under our long-term incentive programs and (ii) the open market purchase by the trustee of 4,862 shares of common stock in connection with the reinvestment of dividends paid on common stock held in trust for employees who were granted performance share awards and who deferred receipt of such awards.

Item 3. Defaults Upon Senior Securities

None.

Item 4. Mine Safety Disclosures

Not applicable.

Item 5. Other Information

None.

Item 6. Exhibits

Exhibit 10.1	-	Amendment No. 3 to the Pfizer Supplemental Savings Plan.
Exhibit 15	-	Accountants' Acknowledgment.
Exhibit 31.1	-	Certification by the Chief Executive Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
Exhibit 31.2	-	Certification by the Chief Financial Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
Exhibit 32.1	-	Certification by the Chief Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
Exhibit 32.2	-	Certification by the Chief Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
Exhibit 101:		
EX-101.INS		XBRL Instance Document
EX-101.SCH		XBRL Taxonomy Extension Schema
EX-101.CAL		XBRL Taxonomy Extension Calculation Linkbase
EX-101.LAB		XBRL Taxonomy Extension Label Linkbase
EX-101.PRE		XBRL Taxonomy Extension Presentation Linkbase
EX-101.DEF		XBRL Taxonomy Extension Definition Document

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Pfizer Inc.

(Registrant)

Dated: November 8, 2018

/s/ Loretta V. Cangialosi

Loretta V. Cangialosi, Senior Vice President and Controller
(Principal Accounting Officer and Duly Authorized Officer)

EXHIBIT 10.1

Amendment No. 3 to the

Pfizer Supplemental Savings Plan (the "PSSP")

(Amended and Restated as of January 1, 2016)

* * *

(New material underlined; deletions crossed out)

1. New Appendix G is added to read as follows:

APPENDIX G

SPECIAL PROVISIONS APPLICABLE TO LEGACY EMPLOYEES TRANSFERRED TO EMPLOYMENT WITH ALLOGENE THERAPEUTICS, INC.

Effective as of April 30, 2018, this Appendix G sets out the additional provisions that apply to those certain employees of the Company (the "Legacy Allogene Employees") whose employment is transferred as of April 30, 2018, May 10, 2018, May 15, 2018 and May 30, 2018 (for each Legacy Employee as applicable, the "Termination Date") to Allogene Therapeutics, Inc. pursuant to that certain Asset Contribution Agreement (the "Agreement"), dated April 2, 2018, by and between Pfizer Inc., a Delaware corporation ("Company"), and Allogene Therapeutics, Inc., a Delaware corporation ("Allogene"):

1. The definition of Regular Earnings under the Plan for Legacy Allogene Employees shall have the meaning as set forth in the Qualified Plan, except that for clarification purposes, with respect to Legacy Allogene Employees who are eligible to defer their bonus under the Pfizer Deferred Compensation Plan, the limitations on the definition of Regular Earnings for any Legacy Allogene Employees set forth in Article XXXII of the Qualified Plan shall also include any deferred bonuses. For Legacy Allogene Employees, any prorated portion of an annual target bonus for 2018 paid (including if deferred) in accordance with the Agreement shall be considered Regular Earnings.

2. For Legacy Allogene Employees, for purposes of any Matching Contribution paid with respect to the 2018 plan year, the applicable Termination Date for each Legacy Employee shall be considered to have occurred on the last day of the second quarter of 2018.

3. For Legacy Allogene Employees, for purposes of the Retirement Savings Contribution paid with respect to the 2018 plan year, the applicable Termination Date for each Legacy Employee shall be considered to have occurred on the last day of 2018. For purposes of clarification, with respect to any Legacy Allogene Employee eligible under the Pfizer Consolidated Pension Plan on December 31, 2017 (the "Pension Transfers"), the Retirement Savings Contribution shall not include bonuses paid reflecting services performed by the Pension Transfer in 2017 and paid in 2018.

4. Effective as of the applicable Termination Date for each Legacy Employee, any unvested Retirement Savings Contributions in the Accounts of Legacy Allogene Employees shall be vested.

Accountant's Acknowledgment

To the Board of Directors and the Shareholders of Pfizer Inc.:

We hereby acknowledge our awareness of the use therein of our report dated November 8, 2018 , included within the Quarterly Report on Form 10-Q of Pfizer Inc. for the quarter ended September 30, 2018 in the following Registration Statements:

-Form S-8 dated October 27, 1983 (File No. 2-87473),
-Form S-8 dated March 22, 1990 (File No. 33-34139),
-Form S-8 dated January 24, 1991 (File No. 33-38708),
-Form S-8 dated November 18, 1991 (File No. 33-44053),
-Form S-8 dated May 27, 1993 (File No. 33-49631),
-Form S-8 dated May 19, 1994 (File No. 33-53713),
-Form S-8 dated October 5, 1994 (File No. 33-55771),
-Form S-8 dated December 20, 1994 (File No. 33-56979),
-Form S-8 dated March 29, 1996 (File No. 333-02061),
-Form S-8 dated September 25, 1997 (File No. 333-36371),
-Form S-8 dated June 19, 2000 (File No. 333-39606),
-Form S-8 dated April 27, 2001 (File No. 333-59660),
-Form S-8 dated April 16, 2003 (File No. 333-104582),
-Form S-8 dated November 18, 2003 (File No. 333-110571),
-Form S-8 dated December 18, 2003 (File No. 333-111333),
-Form S-8 dated April 26, 2004 (File No. 333-114852),
-Form S-8 dated March 1, 2007 (File No. 333-140987),
-Form S-4 dated March 27, 2009 (File No. 333-158237),
-Form S-8 dated October 16, 2009 (File No. 333-162519),
-Form S-8 dated October 16, 2009 (File No. 333-162520),
-Form S-8 dated October 16, 2009 (File No. 333-162521),
-Form S-8 dated March 1, 2010 (File No. 333-165121),
-Form S-8 dated March 2, 2015 (File No. 333-202437),
-Form S-4 dated September 3, 2015 (File No. 333-206758), and
-Form S-3ASR dated February 26, 2018 (File No. 333-223221).

Pursuant to Rule 436 under the Securities Act of 1933 (the Act), such report is not considered a part of a registration statement prepared or certified by an independent registered public accounting firm, or a report prepared or certified by an independent registered public accounting firm within the meaning of Sections 7 and 11 of the Act.

/s/ KPMG LLP
New York, New York
November 8, 2018

EXHIBIT 31.1

Certification by the Chief Executive Officer Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Ian C. Read, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Pfizer Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2018

/s/ IAN C. READ

Ian C. Read

Chairman and Chief Executive Officer

EXHIBIT 31.2

Certification by the Chief Financial Officer Pursuant to
Section 302 of the Sarbanes-Oxley Act of 2002

I, Frank A. D'Amelio, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Pfizer Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2018

/s/ FRANK A. D'AMELIO

Frank A. D'Amelio

Executive Vice President, Business Operations and Chief Financial Officer

EXHIBIT 32.1

Certification by the Chief Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

Pursuant to 18 U.S.C. Section 1350, I, Ian C. Read, hereby certify that, to the best of my knowledge, the Quarterly Report on Form 10-Q of Pfizer Inc. for the fiscal quarter ended September 30, 2018 (the "Report") fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, and that the information contained in that Report fairly presents, in all material respects, the financial condition and results of operations of Pfizer Inc.

/s/ IAN C. READ

Ian C. Read

Chairman and Chief Executive Officer

November 8, 2018

This certification accompanies this Quarterly Report on Form 10-Q pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 and shall not, except to the extent required by such Act, be deemed filed by the Company for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent that the Company specifically incorporates it by reference.

EXHIBIT 32.2

Certification by the Chief Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

Pursuant to 18 U.S.C. Section 1350, I, Frank A. D'Amelio, hereby certify that, to the best of my knowledge, the Quarterly Report on Form 10-Q of Pfizer Inc. for the fiscal quarter ended September 30, 2018 (the "Report") fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, and that the information contained in that Report fairly presents, in all material respects, the financial condition and results of operations of Pfizer Inc.

/s/ FRANK A. D'AMELIO

Frank A. D'Amelio

Executive Vice President, Business Operations and Chief Financial Officer

November 8, 2018

This certification accompanies this Quarterly Report on Form 10-Q pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 and shall not, except to the extent required by such Act, be deemed filed by the Company for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent that the Company specifically incorporates it by reference.

EXHIBIT 4

National Drug Code Directory

Current through March 20, 2019

You have searched Finished drug products

Search Results: *'nivestym'*

Back to Search Page () | Search Again ()

Display 50 **records per page** **Search for text in the table:**

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description
Nivestym	0069-0293-10	300 ug/mL	INJECTION, SOLUTION	INTRAVENOUS; SUBCUTANEOUS	BLA761080	Pfizer Laboratories Div Pfizer Inc	0069-0293	filgrastim-aafi	FILGRASTIM	HUMAN PRESCRIPTION DRUG	03/11/2019	N/A	BLA	10 VIAL, SINGLE-DOSE in 1 CARTON (0069-0293-10) > 1 mL in VIAL, SINGLE DOSE (0069-0293-01)

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description
Nivestym	0069-0294-10	480 ug/1.6mL	INJECTION, SOLUTION	INTRAVENOUS; SUBCUTANEOUS	BLA761080	Pfizer Laboratories Div Pfizer Inc	0069-0294	filgrastim-aafi	FILGRASTIM	HUMAN PRESCRIPTION DRUG	03/11/2019	N/A	BLA	10 VIAL, SINGLE-DOSE in 1 CARTON (0069-0294-10) > 1.6 mL 1 VIAL, SINGLE-DOSE (0069-0294-01)
Nivestym	0069-0292-10	480 ug/.8mL	INJECTION, SOLUTION	SUBCUTANEOUS	BLA761080	Pfizer Laboratories Div Pfizer Inc	0069-0292	filgrastim-aafi	FILGRASTIM	HUMAN PRESCRIPTION DRUG	09/24/2018	N/A	BLA	10 CARTON i 1 CARTON (0069-0292-10) > 1 SYRINGE in CARTON (0069-0292-01) > .8 mL ir 1 SYRINGE
Nivestym	0069-0291-01	300 ug/.5mL	INJECTION, SOLUTION	SUBCUTANEOUS	BLA761080	Pfizer Laboratories Div Pfizer Inc	0069-0291	filgrastim-aafi	FILGRASTIM	HUMAN PRESCRIPTION DRUG	09/24/2018	N/A	BLA	1 SYRINGE i 1 CARTON (0069-0291-01) > .5 mL ir 1 SYRINGE

Proprietary Name	NDC Package Code	Strength	Dosage Form	Route	Appl. No.	Labeler Name	Product NDC	Nonproprietary Name	Substance Name	Product Type Name	Start Marketing Date	End Marketing Date	Market Category	Package Description
Nivestym	0069-0292-01	480 ug/.8mL	INJECTION, SOLUTION	SUBCUTANEOUS	BLA761080	Pfizer Laboratories Div Pfizer Inc	0069-0292	filgrastim-aafi	FILGRASTIM	HUMAN PRESCRIPTION DRUG	09/24/2018	N/A	BLA	1 SYRINGE i 1 CARTON (0069-0292-01) > .8 mL ir 1 SYRINGE
Nivestym	0069-0291-10	300 ug/.5mL	INJECTION, SOLUTION	SUBCUTANEOUS	BLA761080	Pfizer Laboratories Div Pfizer Inc	0069-0291	filgrastim-aafi	FILGRASTIM	HUMAN PRESCRIPTION DRUG	09/24/2018	N/A	BLA	10 CARTON i 1 CARTON (0069-0291-10) > 1 SYRINGE in CARTON (0069-0291-01) > .5 mL ir 1 SYRINGE

Showing 1 to 6 of 6 entries

Previous 1 Next

Background Information (https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm)

Drug questions email: **DRUGINFO@FDA.HHS.GOV (mailto:DRUGINFO@FDA.HHS.Gov)**

See also: **Drug Registration and Listing Instructions (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm)**
National Drug Code Directory Data Files (https://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm)

U.S Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services

EXHIBIT 5

Pfizer Launches Biosimilar Filgrastim, Nivestym, at a Substantial Discount

Pfizer indicated that Nivestym will be priced at a wholesale acquisition cost (WAC) of $350.40 per 480-mcg prefilled syringe, a WAC that is 30.3% lower than that of the reference Neupogen.

Kelly Davio

October 03, 2018

A representative from Pfizer told The Center for Biosimilars® in an email that Nivestym, an FDA-approved biosimilar filgrastim (referencing Neupogen), became commercially available in the United States on October 1. Pfizer began shipping the biosimilar to wholesalers on September 24.

Pfizer indicated that Nivestym will be priced at a wholesale acquisition cost (WAC) of $350.40 per 480-mcg prefilled syringe, a WAC that is 30.3% lower than that of the reference Neupogen, 20.3% lower than that of Zarxio (Sandoz's biosimilar filgrastim), and 14.1% lower than that of Granix (or tbo-filgrastim, Teva's follow-on filgrastim product cleared by the FDA prior to the establishment of a biosimilar approval pathway).

Read more about Nivestym.

Nivestym, like its reference, is a granulocyte-colony stimulating factor that is approved to treat neutropenia in patients who are undergoing myelosuppressive chemotherapy or who have other types of severe neutropenia, and to mobilize autologous hematopoietic progenitor cells into peripheral blood for leukapheresis.

While the United States has 12 approved biosimilar products, Nivestym is only the fifth such product to

Related Content

Study: Biosimilar Filgrastim Can Improve Patient Access to FN Prophylaxis

FDA Approves Second Neupogen Biosimilar, Nivestym

Patient-Administered Biosimilar and Follow-On Filgrastim Pose Opportunity for Savings

launch; some biosimilar products, such as Sandoz's etanercept, Erelzi, or Amgen's adalimumab, Amjevita, have yet to launch despite having been approved in 2016, due in part to a complex patent landscape and ongoing legal challenges.

However, if recent trends are an indication of the future of the marketplace, patients may be able to access biosimilars—and health systems may be able to reap cost savings—sooner. It took Pfizer mere months to launch Nivestym, which was approved in July 2018. Similarly, Mylan and Biocon's pegfilgrastim biosimilar, Fulphila, was approved in June 2018 and launched just 1 month later in July.

Intellisphere, LLC
2 Clarke Drive
Suite 100
Cranbury, NJ 08512

P: 609-716-7777
F: 609-716-4747

EXHIBIT 6

Pfizer Launches Nivestym At An Aggressive Discount To Other Filgrastim Products

02 Oct 2018 | **NEWS**

by Jessica Merrill | @Jessicaemerrill | Jessica.merrill@informa.com

Executive Summary

Pfizer is launching its second US biosimilar, a version of filgrastim, at an aggressive 30.3% discount to Amgen's branded Neupogen and at a discount to competing biosimilars.

Pfizer Inc. is launching a biosimilar version of Amgen Inc.'s granulocyte colony stimulating factor *Neupogen* (filgrastim) in the US at an aggressive discount to the brand and other cheaper versions of the drug. The company announced its biosimilar *Nivestym* (filgrastim-aafi) is available on the market as of Oct. 1.

Nivestym, approved by the FDA in July, joins a crowded filgrastim market that already includes two copycat products, so it makes sense that Pfizer would compete aggressively on price. The product will be priced at a wholesale acquisition cost of $350.40 for the 480 mcg prefilled syringe, a price that is 30.3% lower than the WAC of Neupogen, according to Pfizer.

The Nivestym price is also lower than WAC of Sandoz International GMBH's biosimilar *Zarxio* (filgrastim-sndz) by about 20.3% and Teva Pharmaceutical Industries Ltd.'s follow-on product *Granix* (tbo-filgrastim) by 14.1%. Granix was approved through a traditional BLA pathway rather than the biosimilar pathway. The WAC price does not reflect the impact of rebates and discounts, so it is unclear how the prices stack up after discounts.

The filgrastim biosimilar market has had more time to mature than some other biosimilar categories. Zarxio was the first biosimilar approved in the US, in 2015.
(Also see "Novartis/Sandoz make history with 1st US biosimilar Zarxio" - Scrip, 6 Mar, 2015.) Granix was approved by FDA in 2012. Some payers, including the pharmacy benefit manager Express Scripts Holding Co., have granted the products preferred formulary coverage over branded Neupogen. (Also see "Express Scripts Rewards Low List-Priced Brands In 2019 Formulary, Retains Focus On Rebates" - Scrip, 7 Aug, 2018.)

The category is one where biosimilars have had bigger impact than some other markets. Indeed, the alternatives have taken over the majority of the market share; Neupogen held only a 37% share of the filgrastim market at the end of the second quarter, according to Amgen.

The experience with filgrastim is different than what Pfizer has had with its first US biosimilar, *Inflectra* (infliximab-dyyb), a version of Johnson & Johnson's *Remicade* (infliximab), which launched in 2016 with Celltrion Inc.. J&J has held onto roughly a 94% share of the infliximab market, despite the availability of two biosimilars, relying on a fierce rebating strategy. (Also see "Payers Like Biosimilars, But Rebates Remain The Bottom Line (For Now)" - Scrip, 29 Nov, 2017.) Pfizer is challenging J&J's rebating practices for Remicade in a lawsuit.

It seems Pfizer has learned some lessons from the disappointing launch of its first US biosimilar, however. The company launched Inflectra at a 15% discount to the wholesale acquisition cost of Remicade when it debuted in November 2016. (Also see "Pfizer Will Support Inflectra Launch With Dedicated Sales Force" - Scrip, 14 Nov, 2016.)) Some payers at the time said the discount wasn't steep enough for what they were expecting biosimilars to deliver.

EXHIBIT 7

BioPharma -Reporter.com

Pfizer challenges Amgen with fourth biosimilar approval in US

By Flora Southey

24-Jul-2018 - Last updated on 24-Jul-2018 at 14:12 GMT

RELATED TAGS: Pfizer, Amgen, Sandoz, Biosimilars, Fda

Just days after the release of its Biosimilar Action Plan to encourage generic competition, the US FDA has approved another biosimilar product: Pfizer's answer to Amgen's Neupogen, 'Nivestym'.

Nivestym (filgrastim-aafi) was approved for all eligible indications of the reference product, including to decrease the incidence of infection in patients with non-myeloid malignancies, and to reduce the time to neutrophil recovery and duration of fever in patients with acute myeloid leukaemia.

The product was first approved by the European Medicines Agency in 2010, and has since received the regulatory green light in more than 50 countries.

This latest approval marks the US Food and Drug Administration's (FDA) second for a biosimilar version of Amgen's Neupogen (filgrastim), following Sandoz's Zarxio (filgrastim-sndz) in 2015.

According to Pfizer, *"Nivestym is expected to be available in the US at a significant discount to the current wholesale acquisition cost of Neupogen."*

While Pfizer spokesperson Thomas Biegi did not disclose specific pricing or commercialisation strategies, he told us *"the availability of biosimilars to the market will create competition and drive value."*

The approval comes just days after the FDA issued its Biosimilar Action Plan, as part of a greater strategy to encourage and reward biologics development, and promote biosimilar competition.

In response to the document, a Pfizer spokesperson told us: *"The Biosimilars Action Plan is an important step forward to cultivating a robust biosimilars market in the US with the potential to improve the lives of millions of Americans.*

"But more work needs to be done to tear down market barriers to biosimilars and it will require cooperation from a robust coalition of stakeholders: from Congress and insurers to the FDA, to biologics manufacturers, and the middle-men."

The addition of Nivestym brings Pfizer's biosimilar approval count to four in the US: Inflectra (infliximab) in 2016, Ixifi (infliximab-qbtx) in 2017 – both of which are alternatives to J&J's Remicade – and its biosimilar

version of Amgen's Epogen, Retacrit (epoetin alfa-epbx), approved in May 2018.

RELATED TOPICS: Markets & Regulations, Biosimilars

EXHIBIT 8

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEUPOGEN safely and effectively. See full prescribing information for NEUPOGEN.

NEUPOGEN® (filgrastim) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 1991

----------RECENT MAJOR CHANGES----------
Warnings and Precautions: Aortitis (5.15) 06/2018

----------INDICATIONS AND USAGE----------
NEUPOGEN is a leukocyte growth factor indicated to
- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1.5)
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) (1.6)

----------DOSAGE AND ADMINISTRATION----------
- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.1)
- Patients with cancer undergoing bone marrow transplantation
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy
  - 10 mcg/kg/day subcutaneous injection (2.3)
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis (2.3)
- Patients with congenital neutropenia
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily (2.4)
- Patients with cyclic or idiopathic neutropenia
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily (2.4)
- Patients acutely exposed to myelosuppressive doses of radiation
  - 10 mcg/kg/day subcutaneous injection (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Vial
- Injection: 300 mcg/mL in a single-dose vial (3)
- Injection: 480 mcg/1.6 mL in a single-dose vial (3)

Prefilled Syringe
- Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe (3)
- Injection: 480 mcg/0.8 mL in a single-dose prefilled syringe (3)

----------CONTRAINDICATIONS----------
Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim. (4)

----------WARNINGS AND PRECAUTIONS----------
- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue NEUPOGEN in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue NEUPOGEN in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of NEUPOGEN if causality is likely. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions in patients:
- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea. (6.1)
- With AML (≥ 2% difference in incidence) are pain, epistaxis and rash. (6.1)
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash. (6.1)
- Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia and headache. (6.1)
- With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

NEUPOGEN is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever *[see Clinical Studies (14.1)]*.

1.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

NEUPOGEN is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) *[see Clinical Studies (14.2)]*.

1.3 Patients with Cancer Undergoing Bone Marrow Transplantation

NEUPOGEN is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation *[see Clinical Studies (14.3)]*.

1.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

NEUPOGEN is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis *[see Clinical Studies (14.4)]*.

1.5 Patients with Severe Chronic Neutropenia

NEUPOGEN is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia *[see Clinical Studies (14.5)]*.

1.6 Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

NEUPOGEN is indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation *[see Clinical Studies (14.6)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML

The recommended starting dosage of NEUPOGEN is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes) , or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting NEUPOGEN therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping NEUPOGEN if the ANC increases beyond 10,000/mm^3 *[see Warnings and Precautions (5.10)]*.

Administer NEUPOGEN at least 24 hours after cytotoxic chemotherapy. Do not administer NEUPOGEN within the 24-hour period prior to chemotherapy *[see Warnings and Precautions (5.13)]*. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of NEUPOGEN therapy.

Therefore, to ensure a sustained therapeutic response, administer NEUPOGEN daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of NEUPOGEN therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

2.2 Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation

The recommended dosage of NEUPOGEN following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of NEUPOGEN at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of NEUPOGEN against the neutrophil response (see Table 1).

Table 1. Recommended Dosage Adjustments During Neutrophil Recovery in Patients with Cancer Following BMT

Absolute Neutrophil Count	NEUPOGEN Dosage Adjustment
When ANC greater than 1,000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
Then, if ANC remains greater than 1,000/mm^3 for 3 more consecutive days	Discontinue NEUPOGEN
Then, if ANC decreases to less than 1,000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to less than 1,000/mm^3 at any time during the 5 mcg/kg/day administration, increase NEUPOGEN to 10 mcg/kg/day, and then follow the above steps.

2.3 Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The recommended dosage of NEUPOGEN for the mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer NEUPOGEN for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of NEUPOGEN administration and leukapheresis schedule have not been established, administration of NEUPOGEN for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective *[see Clinical Studies (14.4)]*. Monitor neutrophil counts after 4 days of NEUPOGEN, and discontinue NEUPOGEN if the white blood cell (WBC) count rises to greater than 100,000/mm^3.

2.4 Dosage in Patients with Severe Chronic Neutropenia

Prior to starting NEUPOGEN in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of NEUPOGEN prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommended starting dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection.

<u>Dosage Adjustments in Patients with Severe Chronic Neutropenia</u>
Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN postmarketing surveillance study, the reported median daily doses of NEUPOGEN were: 6 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of NEUPOGEN greater than or equal to 100 mcg/kg/day.

Monitor CBCs for Dosage Adjustments
During the initial 4 weeks of NEUPOGEN therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended.

2.5 Dosage in Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

The recommended dose of NEUPOGEN is 10 mcg/kg as a single daily subcutaneous injection for patients exposed to myelosuppressive doses of radiation. Administer NEUPOGEN as soon as possible after suspected or confirmed exposure to radiation doses greater than 2 gray (Gy).

Estimate a patient's absorbed radiation dose (i.e., level of radiation exposure) based on information from public health authorities, biodosimetry if available, or clinical findings such as time to onset of vomiting or lymphocyte depletion kinetics.

Obtain a baseline CBC and then serial CBCs approximately every third day until the ANC remains greater than 1,000/mm^3 for 3 consecutive CBCs. Do not delay administration of NEUPOGEN if a CBC is not readily available.

Continue administration of NEUPOGEN until the ANC remains greater than 1,000/mm^3 for 3 consecutive CBCs or exceeds 10,000/mm^3 after a radiation-induced nadir.

2.6 Important Administration Instructions

NEUPOGEN is supplied in single-dose vials (for subcutaneous use or intravenous infusion) and single-dose prefilled syringes (for subcutaneous use) *[see Dosage Forms and Strengths (3)]*. Prior to use, remove the vial or prefilled syringe from the refrigerator and allow NEUPOGEN to reach room temperature for a minimum of 30 minutes and a maximum of 24 hours. Discard any vial or prefilled syringe left at room temperature for greater than 24 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit (the solution is clear and colorless). Do not administer NEUPOGEN if particulates or discoloration are observed.

Discard unused portion of NEUPOGEN in vials or prefilled syringes; do not re-enter the vial. Do not save unused drug for later administration.

Subcutaneous Injection
Inject NEUPOGEN subcutaneously in the outer area of upper arms, abdomen, thighs, or upper outer areas of the buttock. If patients or caregivers are to administer NEUPOGEN, instruct them in appropriate injection technique and ask them to follow the subcutaneous injection procedures in the *Instructions for Use* for the vial or prefilled syringe *[see Patient Counseling Information (17)]*.

Training by the healthcare provider should aim to demonstrate to those patients and caregivers how to measure the dose of NEUPOGEN, and the focus should be on ensuring that a patient or caregiver can successfully perform all the steps in the Instructions for Use for the vial or prefilled syringe. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of NEUPOGEN or whether the patient would benefit from a different NEUPOGEN presentation. If a patient or caregiver experiences difficulty measuring the required dose, especially if it is other than the entire contents of the NEUPOGEN prefilled syringe, use of the NEUPOGEN vial may be considered.

If the patient or caregiver misses a dose of NEUPOGEN, instruct them to contact their healthcare provider.

Administration Instructions for the Prefilled Syringe
Persons with latex allergies should not administer the NEUPOGEN prefilled syringe, because the needle cap contains dry natural rubber (derived from latex).

Administration Instructions for Dilution (Vial Only)
If required for intravenous administration, NEUPOGEN (vial only) may be diluted in 5% Dextrose Injection, USP from a concentration of 300 mcg/mL to 5 mcg/mL (do not dilute to a final concentration less than 5 mcg/mL). NEUPOGEN diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% Dextrose Injection, USP or 5% Dextrose plus Albumin (Human), NEUPOGEN is compatible with glass bottles, polyvinyl chloride (PVC) and polyolefin intravenous bags, and polypropylene syringes. **Do not dilute with saline at any time because the product may precipitate.**

Diluted NEUPOGEN solution can be stored at room temperature for up to 24 hours. This 24-hour time period includes the time during room temperature storage of the infusion solution and the duration of the infusion.

3 DOSAGE FORMS AND STRENGTHS

NEUPOGEN is a clear, colorless, preservative-free solution available as:

Vial:
- Injection: 300 mcg/mL in a single-dose vial
- Injection: 480 mcg/1.6 mL in a single-dose vial

Prefilled Syringe:
- Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe
- Injection: 480 mcg/0.8 mL in a single-dose prefilled syringe

4 CONTRAINDICATIONS

NEUPOGEN is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of NEUPOGEN. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving NEUPOGEN. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue NEUPOGEN in patients with ARDS.

5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, have been reported in patients receiving NEUPOGEN. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving NEUPOGEN can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue NEUPOGEN in

patients with serious allergic reactions. NEUPOGEN is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim.

5.4 Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim products. Discontinue NEUPOGEN if sickle cell crisis occurs.

5.5 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving NEUPOGEN. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of NEUPOGEN. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of NEUPOGEN.

5.6 Alveolar Hemorrhage and Hemoptysis

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in NEUPOGEN-treated healthy donors undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of NEUPOGEN. The use of NEUPOGEN for PBPC mobilization in healthy donors is not an approved indication.

5.7 Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after G-CSF administration, including NEUPOGEN, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.8 Patients with Severe Chronic Neutropenia

Confirm the diagnosis of SCN before initiating NEUPOGEN therapy.

Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with NEUPOGEN for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of NEUPOGEN on the development of abnormal cytogenetics and the effect of continued NEUPOGEN administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing NEUPOGEN should be carefully considered.

5.9 Thrombocytopenia

Thrombocytopenia has been reported in patients receiving NEUPOGEN. Monitor platelet counts.

5.10 Leukocytosis

Patients with Cancer Receiving Myelosuppressive Chemotherapy

White blood cell counts of $100{,}000/mm^3$ or greater were observed in approximately 2% of patients receiving NEUPOGEN at dosages above 5 mcg/kg/day. In patients with cancer receiving NEUPOGEN as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is

recommended that NEUPOGEN therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy. Dosages of NEUPOGEN that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit. In patients with cancer receiving myelosuppressive chemotherapy, discontinuation of NEUPOGEN therapy usually resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Peripheral Blood Progenitor Cell Collection and Therapy
During the period of administration of NEUPOGEN for PBPC mobilization in patients with cancer, discontinue NEUPOGEN if the leukocyte count rises to > 100,000/mm^3.

5.11 Cutaneous Vasculitis

Cutaneous vasculitis has been reported in patients treated with NEUPOGEN. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term NEUPOGEN therapy. Hold NEUPOGEN therapy in patients with cutaneous vasculitis. NEUPOGEN may be started at a reduced dose when the symptoms resolve and the ANC has decreased.

5.12 Potential Effect on Malignant Cells

NEUPOGEN is a growth factor that primarily stimulates neutrophils. The granulocyte colony-stimulating factor (G-CSF) receptor through which filgrastim acts has also been found on tumor cell lines. The possibility that filgrastim acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim in chronic myeloid leukemia (CML) and myelodysplasia has not been established.

When NEUPOGEN is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells has not been well studied, and the limited data available are inconclusive.

5.13 Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended

The safety and efficacy of NEUPOGEN given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use NEUPOGEN in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy *[see Dosage and Administration (2.2)]*.

The safety and efficacy of NEUPOGEN have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of NEUPOGEN with chemotherapy and radiation therapy.

5.14 Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

5.15 Aortitis

Aortitis has been reported in patients receiving NEUPOGEN. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue NEUPOGEN if aortitis is suspected.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture *[see Warnings and Precautions (5.1)]*
- Acute Respiratory Distress Syndrome *[see Warnings and Precautions (5.2)]*
- Serious Allergic Reactions *[see Warnings and Precautions (5.3)]*
- Sickle Cell Disorders *[see Warnings and Precautions (5.4)]*
- Glomerulonephritis *[see Warnings and Precautions (5.5)]*
- Alveolar Hemorrhage and Hemoptysis *[see Warnings and Precautions (5.6)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.7)]*
- Thrombocytopenia *[see Warnings and Precautions (5.9)]*
- Leukocytosis *[see Warnings and Precautions (5.10)]*
- Cutaneous Vasculitis *[see Warnings and Precautions (5.11)]*
- Aortitis *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy
The following adverse reaction data in Table 2 are from three randomized, placebo-controlled studies in patients with:

- small cell lung cancer receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide (Study 1)
- small cell lung cancer receiving ifosfamide, doxorubicin, and etoposide (Study 2), and
- non-Hodgkin's lymphoma (NHL) receiving doxorubicin, cyclophosphamide, vindesine, bleomycin, methylprednisolone, and methotrexate ("ACVBP") or mitoxantrone, ifosfamide, mitoguazone, teniposide, methotrexate, folinic acid, methylprednisolone, and methotrexate ("VIM3") (Study 3).

A total of 451 patients were randomized to receive subcutaneous NEUPOGEN 230 mcg/m^2 (Study 1), 240 mcg/m^2 (Study 2) or 4 or 5 mcg/kg/day (Study 3) (n = 294) or placebo (n = 157). The patients in these studies were median age 61 (range 29 to 78) years and 64% were male. The ethnicity was 95% Caucasian, 4% African American, and 1% Asian.

Table 2. Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy (With ≥ 5% Higher Incidence in NEUPOGEN Compared to Placebo)

System Organ Class Preferred Term	NEUPOGEN (N = 294)	Placebo (N = 157)
Blood and lymphatic system disorders		
Thrombocytopenia	38%	29%
Gastrointestinal disorders		
Nausea	43%	32%
General disorders and administration site conditions		
Pyrexia	48%	29%
Chest pain	13%	6%
Pain	12%	6%
Fatigue	20%	10%
Musculoskeletal and connective tissue disorders		
Back pain	15%	8%
Arthralgia	9%	2%

Bone pain	11%	6%
Pain in extremity*	7%	3%
Nervous system disorders		
Dizziness	14%	3%
Respiratory, thoracic and mediastinal disorders		
Cough	14%	8%
Dyspnea	13%	8%
Skin and subcutaneous tissue disorders		
Rash	14%	5%
Investigations		
Blood lactate dehydrogenase increased	6%	1%
Blood alkaline phosphatase increased	6%	1%

* Percent difference (NEUPOGEN – Placebo) was 4%.

Adverse events with ≥ 5% higher incidence in NEUPOGEN patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy delivered included anemia, constipation, diarrhea, oral pain, vomiting, asthenia, malaise, edema peripheral, hemoglobin decreased, decreased appetite, oropharyngeal pain, and alopecia.

Adverse Reactions in Patients with Acute Myeloid Leukemia

Adverse reaction data below are from a randomized, double-blind, placebo-controlled study in patients with AML (Study 4) who received an induction chemotherapy regimen of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5 and up to 3 additional courses of therapy (induction 2, and consolidation 1, 2) of intravenous daunorubicin, cytosine arabinoside, and etoposide. The safety population included 518 patients randomized to receive either 5 mcg/kg/day NEUPOGEN (n = 257) or placebo (n = 261). The median age was 54 (range 16 to 89) years and 54% were male.

Adverse reactions with ≥ 2% higher incidence in NEUPOGEN patients compared to placebo included epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular.

Adverse events with ≥ 2% higher incidence in NEUPOGEN patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy included diarrhea, constipation, and transfusion reaction.

Adverse Reactions in Patients with Cancer Undergoing Bone Marrow Transplantation

The following adverse reaction data are from one randomized, no treatment-controlled study in patients with acute lymphoblastic leukemia or lymphoblastic lymphoma receiving high-dose chemotherapy (cyclophosphamide or cytarabine, and melphalan) and total body irradiation (Study 5) and one randomized, no treatment-controlled study in patients with Hodgkin's disease (HD) and NHL undergoing high-dose chemotherapy and autologous bone marrow transplantation (Study 6). Patients receiving autologous bone marrow transplantation only were included in the analysis. A total of 100 patients received either 30 mcg/kg/day as a 4-hour infusion (Study 5) or 10 mcg/kg/day or 30 mcg/kg/day as a 24-hour infusion (Study 6) NEUPOGEN (n = 72), no treatment control or placebo (n = 28). The median age was 30 (range 15 to 57) years, 57% were male.

Adverse reactions with ≥ 5% higher incidence in NEUPOGEN patients compared to patients receiving no NEUPOGEN included rash and hypersensitivity.

Adverse reactions in patients receiving intensive chemotherapy followed by autologous BMT with ≥ 5% higher incidence in NEUPOGEN patients compared to patients receiving no NEUPOGEN included thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia.

Adverse Reactions in Patients with Cancer Undergoing Autologous Peripheral Blood Progenitor Cell Collection

The adverse reaction data in Table 3 are from a series of 7 trials in patients with cancer undergoing mobilization of autologous peripheral blood progenitor cells for collection by leukapheresis. Patients (n = 166) in all these trials underwent a similar mobilization/collection regimen: NEUPOGEN was

administered for 6 to 8 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dosage of NEUPOGEN ranged between 5 to 30 mcg/kg/day and was administered subcutaneously by injection or continuous infusion. The median age was 39 (range 15 to 67) years, and 48% were male.

Table 3. Adverse Reactions in Patients with Cancer Undergoing Autologous PBPC in the Mobilization Phase (≥ 5% Incidence in NEUPOGEN Patients)

System Organ Class Preferred Term	Mobilization Phase (N = 166)
Musculoskeletal and connective tissue disorders	
Bone pain	30%
General disorders and administration site conditions	
Pyrexia	16%
Investigations	
Blood alkaline phosphatase increased	11%
Nervous system disorders	
Headache	10%

Adverse Reactions in Patients with Severe Chronic Neutropenia

The following adverse reaction data were identified in a randomized, controlled study in patients with SCN receiving NEUPOGEN (Study 7). 123 patients were randomized to a 4-month observation period followed by subcutaneous NEUPOGEN treatment or immediate subcutaneous NEUPOGEN treatment. The median age was 12 years (range 7 months to 76 years) and 46% were male. The dosage of NEUPOGEN was determined by the category of neutropenia. Initial dosage of NEUPOGEN:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dosage was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

Adverse reactions with ≥ 5% higher incidence in NEUPOGEN patients compared to patients receiving no NEUPOGEN included arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, and urinary tract infection (upper respiratory tract infection and urinary tract infection were higher in the NEUPOGEN arm, total infection related events were lower in NEUPOGEN treated patients), epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to filgrastim in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The incidence of antibody development in patients receiving NEUPOGEN has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim, the nature and specificity of these antibodies has not been adequately studied. In clinical studies using NEUPOGEN, the incidence of antibodies binding to filgrastim was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell based bioassay.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of NEUPOGEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions (5.1)]*
- acute respiratory distress syndrome *[see Warnings and Precautions (5.2)]*
- anaphylaxis *[see Warnings and Precautions (5.3)]*
- sickle cell disorders *[see Warnings and Precautions (5.4)]*
- glomerulonephritis *[see Warnings and Precautions (5.5)]*
- alveolar hemorrhage and hemoptysis *[see Warnings and Precautions (5.6)]*
- capillary leak syndrome *[see Warnings and Precautions (5.7)]*
- leukocytosis *[see Warnings and Precautions (5.10)]*
- cutaneous vasculitis *[see Warnings and Precautions (5.11)]*
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- decreased bone density and osteoporosis in pediatric patients receiving chronic treatment with NEUPOGEN
- aortitis *[see Warnings and Precautions (5.15)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published studies, including several observational studies of pregnancy outcomes in women exposed to filgrastim products and those who were unexposed, have not established an association with NEUPOGEN use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes (*see Data*). Reports in the scientific literature have described transplacental passage of NEUPOGEN in pregnant women when administered ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation). In animal reproduction studies, effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations were observed in either species. No maternal or fetal effects were observed in pregnant rats at doses up to 58 times the human doses. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15- 20%, respectively.

Data

Human Data

Several observational studies based on the Severe Chronic Neutropenia International Registry (SCNIR) described pregnancy outcomes in women with severe chronic neutropenia (SCN) who were exposed to filgrastim products during pregnancy and women with SCN who were unexposed. No major differences were seen between treated and untreated women with respect to pregnancy outcome (including miscarriage and preterm labor), newborn complications (including birth weight), and infections. Methodological

limitations of these studies include small sample size and lack of generalizability due to the underlying maternal condition.

Animal Data

Effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations were observed in either species. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses. In pregnant rabbits showing signs of maternal toxicity, reduced embryo-fetal survival (at 20 and 80 mcg/kg/day) and increased abortions (at 80 mcg/kg/day) were observed. In pregnant rats, no maternal or fetal effects were observed at doses up to 575 mcg/kg/day, which is approximately 58 times higher than the human dose of 10 mcg/kg/day.

Offspring of rats administered filgrastim during the peri-natal and lactation periods exhibited a delay in external differentiation and growth retardation (≥ 20 mcg/kg/day) and slightly reduced survival rate (100 mcg/kg/day).

8.2 Lactation

Risk Summary

There is published literature documenting transfer of filgrastim into human milk. There are a few case reports describing the use of filgrastim in breastfeeding mothers with no adverse effects noted in the infants. There are no data on the effects of filgrastim on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEUPOGEN and any potential adverse effects on the breastfed child from NEUPOGEN or from the underlying maternal condition.

8.4 Pediatric Use

In patients with cancer receiving myelosuppressive chemotherapy, 15 pediatric patients median age 2.6 (range 1.2 to 9.4) years with neuroblastoma were treated with myelosuppressive chemotherapy (cyclophosphamide, cisplatin, doxorubicin, and etoposide) followed by subcutaneous NEUPOGEN at doses of 5, 10, or 15 mcg/kg/day for 10 days (n = 5/dose) (Study 8). The pharmacokinetics of NEUPOGEN in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of NEUPOGEN. In this population, NEUPOGEN was well tolerated. There was one report of palpable splenomegaly and one report of hepatosplenomegaly associated with NEUPOGEN therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

The safety and effectiveness of NEUPOGEN have been established in pediatric patients with SCN *[see Clinical Studies (14.5)]*. In a phase 3 study (Study 7) to assess the safety and efficacy of NEUPOGEN in the treatment of SCN, 123 patients with a median age of 12 years (range 7 months to 76 years) were studied. Of the 123 patients, 12 were infants (7 months to 2 years of age), 49 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 731 patients in the surveillance study, 429 were pediatric patients < 18 years of age (range 0.9 to 17) *[see Indications and Usage (1.5), Dosage and Administration (2.6), and Clinical Studies (14.5)]*.

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of NEUPOGEN treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic NEUPOGEN treatment. The relationship of these events to NEUPOGEN administration is unknown *[see Warnings and Precautions (5.8) and Adverse Reactions (6)]*.

The use of NEUPOGEN to increase survival in pediatric patients acutely exposed to myelosuppressive doses of radiation is based on studies conducted in animals and clinical data supporting the use of NEUPOGEN in other approved indications *[see Dosage and Administration (2.1 to 2.4) and Clinical Studies (14.6)]*.

8.5 Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo-controlled trials of NEUPOGEN-treated patients receiving myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Clinical studies of NEUPOGEN in other approved indications (i.e., BMT recipients, PBPC mobilization, and SCN) did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects.

10 OVERDOSAGE

The maximum tolerated dose of NEUPOGEN has not been determined. In NEUPOGEN clinical trials of patients with cancer receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

11 DESCRIPTION

Filgrastim is a 175 amino acid human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology. Filgrastim is produced by *Escherichia coli* (*E coli*) bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. Filgrastim has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E coli*. Because filgrastim is produced in *E coli*, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

NEUPOGEN injection is a sterile, clear, colorless, preservative-free liquid containing filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by a cell mitogenesis assay). The product is available in single-dose vials and prefilled syringes. The single-dose vials contain either 300 mcg/mL or 480 mcg/1.6 mL of filgrastim. The single-dose prefilled syringes contain either 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim. See table below for product composition of each single-dose vial or prefilled syringe.

	300 mcg/mL Vial	**480 mcg/1.6 mL Vial**	**300 mcg/0.5 mL Syringe**	**480 mcg/0.8 mL Syringe**
filgrastim	300 mcg	480 mcg	300 mcg	480 mcg
acetate	0.59 mg	0.94 mg	0.295 mg	0.472 mg
polysorbate 80	0.04 mg	0.064 mg	0.02 mg	0.032 mg
sodium	0.035 mg	0.056 mg	0.0175 mg	0.028 mg
sorbitol	50 mg	80 mg	25 mg	40 mg

water for Injection USP q.s. ad*	1 mL	1.6 mL	0.5 mL	0.8 mL

* quantity sufficient to make

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

Endogenous G-CSF is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production or activity of hematopoietic cell types other than the neutrophil lineage.

12.2 Pharmacodynamics

In phase 1 studies involving 96 patients with various nonmyeloid malignancies, NEUPOGEN administration resulted in a dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 mcg/kg/day. This increase in neutrophil counts was observed whether NEUPOGEN was administered intravenous (1 to 70 mcg/kg twice daily) , subcutaneous (1 to 3 mcg/kg once daily) , or by continuous subcutaneous infusion (3 to 11 mcg/kg/day). With discontinuation of NEUPOGEN therapy, neutrophil counts returned to baseline in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic (measured by migration under agarose using N-formyl-methionyl-leucyl-phenylalanine [fMLP] as the chemotaxin) activity in vitro.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving NEUPOGEN; however, the percentage of monocytes in the differential count remained within the normal range. Absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of NEUPOGEN. Increases in lymphocyte counts following NEUPOGEN administration have been reported in some normal subjects and patients with cancer.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, Dohle bodies, increased granulocyte granulation, and hypersegmented neutrophils have been observed. Such changes were transient and were not associated with clinical sequelae, nor were they necessarily associated with infection.

12.3 Pharmacokinetics

Filgrastim exhibits nonlinear pharmacokinetics. Clearance is dependent on filgrastim concentration and neutrophil count: G-CSF receptor-mediated clearance is saturated by high concentration of NEUPOGEN and is diminished by neutropenia. In addition, filgrastim is cleared by the kidney.

Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg of filgrastim resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. After intravenous administration, the volume of distribution averaged 150 mL/kg and the elimination half-life was approximately 3.5 hours in both normal subjects and cancer subjects. Clearance rates of filgrastim were approximately 0.5 to 0.7 mL/minute/kg. Single parenteral doses or daily intravenous doses, over a 14-day period, resulted in

comparable half-lives. The half-lives were similar for intravenous administration (231 minutes, following doses of 34.5 mcg/kg) and for subcutaneous administration (210 minutes, following NEUPOGEN dosages of 3.45 mcg/kg). Continuous 24-hour intravenous infusions of 20 mcg/kg over an 11 to 20-day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated. The absolute bioavailability of filgrastim after subcutaneous administration is 60% to 70%.

Specific Populations

Patients Acutely Exposed to Myelosuppressive Doses of Radiation

The pharmacokinetics of filgrastim is not available in patients acutely exposed to myelosuppressive doses of radiation. Based on limited pharmacokinetics data in irradiated non-human primates, the area under the time-concentration curve (AUC), reflecting the exposure to filgrastim in non-human primates at 10 mcg/kg dose of NEUPOGEN, appears to be similar to that in humans at 5 mcg/kg. Simulations conducted using the population pharmacokinetic model indicates that the exposures to filgrastim at a NEUPOGEN dose of 10 mcg/kg in patients acutely exposed to myelosuppressive doses of radiation are expected to exceed the exposures at a dose of 10 mcg/kg in irradiated non-human primates.

Pediatric Patients

The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adult patients receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim *[see Use in Specific Populations (8.4)]*.

Renal Impairment

In a study with healthy volunteers, subjects with moderate renal impairment, and subjects with end-stage renal disease (n = 4 per group), higher serum concentrations were observed in subjects with end-stage renal disease. However, dose adjustment in patients with renal impairment is not necessary.

Hepatic Impairment

Pharmacokinetics and pharmacodynamics of filgrastim are similar between subjects with hepatic impairment and healthy subjects (n = 12/group). The study included 10 subjects with mild hepatic impairment (Child-Pugh Class A) and 2 subjects with moderate hepatic impairment (Child-Pugh Class B). Therefore, filgrastim dose adjustment for patients with hepatic impairment is not necessary.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of filgrastim has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. Filgrastim had no observed effect on the fertility of male or female rats at doses up to 500 mcg/kg.

13.2 Animal Toxicology and Pharmacology

Filgrastim was administered to monkeys, dogs, hamsters, rats, and mice as part of a nonclinical toxicology program, which included studies up to 1-year duration.

In the repeated-dose studies, changes observed were attributable to the expected pharmacological actions of filgrastim (i.e., dose-dependent increases in white blood cell counts, increased circulating segmented neutrophils, and increased myeloid:erythroid ratio in bone marrow). Histopathologic examination of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis, and dose-related increases in spleen weight were seen in all species. These changes all reversed after discontinuation of treatment.

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The safety and efficacy of NEUPOGEN to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive NEUPOGEN (n = 99) at a dose of 230 mcg/m^2 (4 to 8 mcg/kg/day) or placebo (n = 111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease.

The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC < 1,000/mm^3 and temperature > 38.2°C. Treatment with NEUPOGEN resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for NEUPOGEN-treated patients and 76% for placebo-treated patients ($p < 0.001$). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm^3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

14.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of NEUPOGEN to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, *de novo* AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous NEUPOGEN (n = 259) at a dose of 5 mcg/kg/day or placebo (n = 262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥ 1,000/mm^3 for 3 consecutive days or ≥ 10,000/mm^3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% < 25,000/mm^3 and 27% > 100,000/mm^3); 29% unfavorable cytogenetics.

The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm^3. Treatment with NEUPOGEN resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, NEUPOGEN-treated patients 14 days, placebo-treated patients 19 days ($p = 0.0001$: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, NEUPOGEN-treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, NEUPOGEN-treated patients: 20 days versus placebo-treated patients: 25 days.

There were no statistically significant differences between the NEUPOGEN and the placebo groups in complete remission rate (69% - NEUPOGEN, 68% - placebo), median time to progression of all randomized patients (165 days - NEUPOGEN, 186 days - placebo), or median overall survival (380 days - NEUPOGEN, 425 days - placebo).

14.3 Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of NEUPOGEN to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of NEUPOGEN to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo-controlled trial (Study 10).

In Study 6, patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, NEUPOGEN 10 mcg/kg/day, and NEUPOGEN 30 mcg/kg/day as a 24-hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's disease and 31% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm^3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) occurred in the NEUPOGEN-treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, $p = 0.004$]).

In Study 9, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion NEUPOGEN 10 mcg/kg/day (n = 19), NEUPOGEN 30 mcg/kg/day (n = 10) and no treatment (n = 14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) in the NEUPOGEN-treated groups versus the control group (21.5 days in the control group versus 10 days in the NEUPOGEN-treated groups, $p < 0.001$). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the NEUPOGEN-treated groups, $p < 0.0001$).

In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive NEUPOGEN 300 mcg/m^2/day (n = 33) or placebo (n = 37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, $p < 0.001$) and time to recovery of ANC to ≥ 500/mm^3 (21 days in the control group and 16 days in the treatment group, $p < 0.001$).

14.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The safety and efficacy of NEUPOGEN to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using NEUPOGEN mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: NEUPOGEN was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of NEUPOGEN ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using NEUPOGEN mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm^3 by day 28. In clinical trials of NEUPOGEN for the mobilization of hematopoietic progenitor cells, NEUPOGEN was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm^3) was reached. The rate of engraftment of these cells in the absence of NEUPOGEN post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received NEUPOGEN-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). Patients received daily NEUPOGEN 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin's disease and 43% non-Hodgkin's lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to NEUPOGEN-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

14.5 Patients with Severe Chronic Neutropenia

The safety and efficacy of NEUPOGEN to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7).

Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm^3 on three occasions during a 6-month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm^3 per cycle. In addition, patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4-month observation period followed by NEUPOGEN treatment or immediate NEUPOGEN treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia.

NEUPOGEN was administered subcutaneously. The dose of NEUPOGEN was determined by the category of neutropenia. Initial dose of NEUPOGEN:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

The main efficacy endpoint was response to NEUPOGEN treatment. ANC response from baseline (< 500/mm^3) was defined as follows:

- Complete response: median ANC > 1,500/mm^3
- Partial response: median ANC ≥ 500/mm^3 and ≤ 1,500/mm^3 with a minimum increase of 100%
- No response: median ANC < 500/mm^3

There were 112 of 123 patients who demonstrated a complete or partial response to NEUPOGEN treatment.

Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving NEUPOGEN of the following parameters:

- incidence of infection

- incidence of fever
- duration of fever
- incidence, duration, and severity of oropharyngeal ulcers
- number of days of antibiotic use

The incidence for each of these 5 clinical parameters was lower in the NEUPOGEN arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although NEUPOGEN substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

14.6 Patients Acutely Exposed to Myelosuppressive Doses of Radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)

Efficacy studies of NEUPOGEN could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval of this indication was based on efficacy studies conducted in animals and data supporting the use of NEUPOGEN for other approved indications *[see Dosage and Administration (2.1 to 2.4)]*.

Because of the uncertainty associated with extrapolating animal efficacy data to humans, the selection of human dose for NEUPOGEN is aimed at providing exposures to filgrastim that exceed those observed in animal efficacy studies. The 10 mcg/kg daily dose is selected for humans exposed to myelosuppressive doses of radiation because the exposure associated with such a dose is expected to exceed the exposure associated with a 10 mcg/kg dose in non-human primates *[see Pharmacokinetics (12.3)]*. The safety of NEUPOGEN at a daily dose of 10 mcg/kg has been assessed on the basis of clinical experience in approved indications.

The efficacy of NEUPOGEN was studied in a randomized, blinded, placebo-controlled study in a non-human primate model of radiation injury. The planned sample size was 62 animals, but the study was stopped at the interim analysis with 46 animals because efficacy was established. Rhesus macaques were randomized to a control (n = 22) or treated (n = 24) group. Animals were exposed to total body irradiation of 7.4 ± 0.15 Gy delivered at 0.8 ± 0.03 Gy/min, representing a dose that would be lethal in 50% of animals by 60 days of follow-up (LD50/60). Starting on day 1 after irradiation, animals received daily subcutaneous injections of placebo (5% dextrose in water) or filgrastim (10 mcg/kg/day). Blinded treatment was stopped when one of the following criteria was met: ANC $\geq$ 1,000/mm^3 for 3 consecutive days, or ANC $\geq$ 10,000/mm^3 for more than 2 consecutive days within study day 1 to 5, or ANC $\geq$ 10,000/mm^3 any time after study day 5. Animals received medical management consisting of intravenous fluids, antibiotics, blood transfusions, and other support as required.

Filgrastim significantly (at 0.023 level of significance) reduced 60-day mortality in the irradiated non-human primates: 21% mortality (5/24) in the filgrastim group compared to 59% mortality (13/22) in the control group.

16 HOW SUPPLIED/STORAGE AND HANDLING

NEUPOGEN injection is a clear, colorless, preservative-free solution supplied as:

Vials
Single-dose vials containing 300 mcg/mL of filgrastim. Dispensing packs of 10 vials (NDC 55513-530-10).

Single-dose vials containing 480 mcg/1.6 mL (300 mcg/mL) of filgrastim. Dispensing packs of 10 vials (NDC 55513-546-10).

Prefilled Syringes (SingleJect®)

Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe® Needle Guard, containing 300 mcg/0.5 mL of filgrastim.

- Pack of 1 prefilled syringe (NDC 55513-924-91).
- Pack of 10 prefilled syringes (NDC 55513-924-10).

Single-dose, prefilled syringe with 27 gauge, ½ inch needle with an UltraSafe® Needle Guard, containing 480 mcg/0.8 mL of filgrastim.

- Pack of 1 prefilled syringe (NDC 55513-209-91).
- Pack of 10 prefilled syringes (NDC 55513-209-10).

The needle cap of the prefilled syringe contains dry natural rubber (a derivative of latex) *[see Dosage and Administration (2.6)]*.

Store NEUPOGEN at 2° to 8°C (36° to 46°F) in the carton to protect from light. Do not leave NEUPOGEN in direct sunlight. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard NEUPOGEN if frozen more than once. Avoid shaking. Transport via a pneumatic tube has not been studied.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). Review the steps for direct patient administration with patients and caregivers. Training by the healthcare provider should aim to ensure that patients and caregivers can successfully perform all of the steps in the Instructions for Use of NEUPOGEN vial and prefilled syringe, including showing the patient or caregiver how to measure the required dose, particularly if a patient is on a dose other than the entire prefilled syringe. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of NEUPOGEN or whether the patient would benefit from a different NEUPOGEN presentation.

Advise patients of the following risks and potential risks with NEUPOGEN:

- Rupture or enlargement of the spleen may occur. Symptoms include left upper quadrant abdominal pain or left shoulder pain. Advise patients to report pain in these areas to their physician immediately *[see Warnings and Precautions (5.1)]*.
- Dyspnea, with or without fever, progressing to Acute Respiratory Distress Syndrome, may occur. Advise patients to report dyspnea to their physician immediately *[see Warnings and Precautions (5.2)]*.
- Serious allergic reactions may occur, which may be signaled by rash, facial edema, wheezing, dyspnea, hypotension, or tachycardia. Advise patients to seek immediate medical attention if signs or symptoms of hypersensitivity reaction occur *[see Warnings and Precautions (5.3)]*.
- In patients with sickle cell disease, sickle cell crisis and death have occurred. Discuss potential risks and benefits for patients with sickle cell disease prior to the administration of human granulocyte colony-stimulating factors *[see Warnings and Precautions (5.4)]*.
- Glomerulonephritis may occur. Symptoms include swelling of the face or ankles, dark colored urine or blood in the urine, or a decrease in urine production. Advise patients to report signs or symptoms of glomerulonephritis to their physician immediately *[see Warnings and Precautions (5.5)]*.
- Cutaneous vasculitis may occur, which may be signaled by purpura or erythema. Advise patients to report signs or symptoms of vasculitis to their physician immediately *[see Warnings and Precautions (5.11)]*.
- Aortitis may occur. Symptoms may include fever, abdominal pain, malaise, back pain, and increased inflammatory markers. Advise patients to report signs and symptoms of aortitis to their physician immediately *[see Warnings and Precautions (5.15)]*.

Advise patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) that efficacy studies of NEUPOGEN for this indication could not be conducted in humans for ethical and feasibility reasons and that, therefore, approval of this use was based on efficacy studies conducted in animals *[see Clinical Studies (14.6)]*.

Instruct patients who self-administer NEUPOGEN using the prefilled syringe or single-dose vial of the:

- Importance of following the applicable Instructions for Use.
- Dangers of reusing needles, syringes, or unused portions of single-dose vials.
- Importance of following local requirements for proper disposal of used syringes, needles, and unused vials.
- Importance of informing the healthcare provider if difficulty occurs when measuring or administering partial contents of the NEUPOGEN prefilled syringe. If difficulty occurs, use of the NEUPOGEN vial may be considered.
- Difference in product concentration of the NEUPOGEN prefilled syringe in comparison to the NEUPOGEN vial. When switching patients from the NEUPOGEN prefilled syringe to the NEUPOGEN vial, or vice versa, ensure that patients understand the correct volume to be administered since the concentration of NEUPOGEN differs between the prefilled syringe and the vial.

AMGEN®

NEUPOGEN® (filgrastim)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License Number 1080

Patent: http://pat.amgen.com/neupogen/

www.NEUPOGEN.com
1-800-77-AMGEN (1-800-772-6436)

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Patient Information
NEUPOGEN® (nu-po-jen)
(filgrastim)
injection

What is NEUPOGEN?

NEUPOGEN is a man-made form of granulocyte colony-stimulating factor (G-CSF). G-CSF is a substance produced by the body. It stimulates the growth of neutrophils, a type of white blood cell important in the body's fight against infection.

Acute Radiation Syndrome: The effectiveness of NEUPOGEN for this use was only studied in animals, because it could not be studied in people.

Do not take NEUPOGEN if you have had a serious allergic reaction to human G-CSFs such as filgrastim or pegfilgrastim products.

Before you take NEUPOGEN, tell your healthcare provider about all of your medical conditions, including if you:

- have a sickle cell disorder.
- have kidney problems.
- are receiving radiation therapy.
- are allergic to latex. The needle cap on the prefilled syringe contains dry natural rubber (derived from latex). You should not give NEUPOGEN using the prefilled syringe if you have latex allergies. Ask your healthcare provider about using the vial if you have latex allergies.
- are pregnant or plan to become pregnant. It is not known if NEUPOGEN will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if NEUPOGEN passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive NEUPOGEN?

- **NEUPOGEN injections can be given by a healthcare provider by intravenous (IV) infusion or under your skin (subcutaneous injection). Your healthcare provider may decide subcutaneous injections can be given at home by you or your caregiver. If NEUPOGEN is given at home, see the detailed "Instructions for Use" that comes with your NEUPOGEN for information on how to prepare and inject a dose of NEUPOGEN.**
- You and your caregiver should be shown how to prepare and inject NEUPOGEN before you use it, by your healthcare provider.
- Your healthcare provider will tell you how much NEUPOGEN to inject and when to inject it. Do not change your dose or stop NEUPOGEN unless your healthcare provider tells you to.
- If you are receiving NEUPOGEN because you are also receiving chemotherapy, your dose of NEUPOGEN should be injected **at least 24 hours before** or **24 hours after** your dose of chemotherapy. Your healthcare provider will do blood tests to monitor your white blood cell count, and if necessary, adjust your NEUPOGEN dose.
- If you are receiving NEUPOGEN because you have been suddenly (acutely) exposed to an amount of radiation that can affect your bone marrow (Acute Radiation Syndrome), you will need to have blood tests about every 3 days during treatment with NEUPOGEN to check your white blood cell count.
- If you miss a dose of NEUPOGEN, talk to your healthcare provider about when you should give your next dose.

What are the possible side effects of NEUPOGEN?

NEUPOGEN may cause serious side effects, including:

- **Spleen rupture.** Your spleen may become enlarged and can rupture. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in the left upper stomach (abdomen) area or your left shoulder.
- **A serious lung problem called acute respiratory distress syndrome (ARDS).** Call your healthcare provider or get emergency medical help right away if you have shortness of breath with or without a fever, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.** NEUPOGEN can cause serious allergic reactions. These reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness, swelling around your mouth or eyes, fast heart rate, and sweating. If you have any of these symptoms, stop using NEUPOGEN and call your healthcare provider or get emergency medical help right away.
- **Sickle cell crises.** You may have a serious sickle cell crisis, which could lead to death, if you have a sickle cell disorder and receive NEUPOGEN. Call your healthcare provider right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.

- **Kidney injury (glomerulonephritis).** NEUPOGEN can cause kidney injury. Call your healthcare provider right away if you develop any of the following symptoms:
  - swelling of your face or ankles
  - blood in your urine or dark colored urine
  - you urinate less than usual
- **Capillary leak syndrome.** NEUPOGEN can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
  - swelling or puffiness and are urinating less than usual
  - trouble breathing
  - swelling of your stomach area (abdomen) and feeling of fullness
  - dizziness or feeling faint
  - a general feeling of tiredness
- **Decreased platelet count (thrombocytopenia).** Your healthcare provider will check your blood during treatment with NEUPOGEN. Tell your healthcare provider if you have unusual bleeding or bruising during treatment with NEUPOGEN. This could be a sign of decreased platelet counts, which may reduce the ability of your blood to clot.
- **Increased white blood cell count (leukocytosis).** Your healthcare provider will check your blood during treatment with NEUPOGEN.
- **Inflammation of your blood vessels (cutaneous vasculitis).** Tell your healthcare provider right away if you develop purple spots or redness of your skin.
- **Inflammation of the aorta (aortitis).** Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported in patients who received NEUPOGEN. Symptoms may include fever, abdominal pain, feeling tired, and back pain. Call your healthcare provider if you experience these symptoms.

The most common side effects experienced in patients receiving NEUPOGEN include:

- Patients with cancer receiving chemotherapy: fever, pain, rash, cough, and shortness of breath
- Patients with acute myeloid leukemia receiving chemotherapy: pain, nose bleed, and rash
- Patients with cancer receiving chemotherapy followed by bone marrow transplant: rash
- Patients who are having their own blood cells collected: bone pain, fever, and headache
- Patients with severe chronic neutropenia: pain, decreased red blood cells, nose bleed, diarrhea, reduced sensation, and hair loss

These are not all the possible side effects of NEUPOGEN. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NEUPOGEN?

- Store NEUPOGEN in the refrigerator between 36˚F to 46˚F (2˚C to 8˚C).
- **Do not** freeze.
- Keep NEUPOGEN in the original carton to protect from light or physical damage. Do not leave NEUPOGEN in direct sunlight.
- Do not shake NEUPOGEN.
- Take NEUPOGEN out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- Throw away (dispose of) any NEUPOGEN that has been left at room temperature for longer than 24 hours.
- After you inject your dose, throw away (dispose of) any unused NEUPOGEN left in the vials or prefilled syringes. **Do not** save unused NEUPOGEN in the vials or prefilled syringes for later use.

Keep NEUPOGEN out of the reach of children.

General information about the safe and effective use of NEUPOGEN.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NEUPOGEN for a condition for which it was not prescribed. Do not give NEUPOGEN to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about NEUPOGEN that is written for healthcare professionals.

What are the ingredients in NEUPOGEN?

Active ingredient: filgrastim
Inactive ingredients: acetate, polysorbate 80, sodium, sorbitol, and water for Injection

Manufactured by:
Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799 U.S.A.
US License No. 1080

AMGEN®

Patent: http://pat.amgen.com/neupogen/

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 06/2018

EXHIBIT 9

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NIVESTYM safely and effectively. See full prescribing information for NIVESTYM.

NIVESTYM™ (filgrastim-aafi) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2018
NIVESTYM (filgrastim-**aafi**) is biosimilar* to NEUPOGEN (filgrastim).

---------- INDICATIONS AND USAGE----------
NIVESTYM is a leukocyte growth factor indicated to
- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. (1.5)

----------DOSAGE AND ADMINISTRATION----------
- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML.
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration. (2.1)
- Patients with cancer undergoing bone marrow transplantation.
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration. (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy.
  - 10 mcg/kg/day subcutaneous injection. (2.3)
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis. (2.3)
- Patients with congenital neutropenia.
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily. (2.4)
- Patients with cyclic or idiopathic neutropenia.
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily. (2.4)
- Direct administration of less than 0.3 mL (180 mcg) using NIVESTYM prefilled syringe is not recommended due to potential for dosing errors. (2.5)

---------- DOSAGE FORMS AND STRENGTHS----------
Vial
- Injection: 300 mcg/mL in a single-dose vial (3)
- Injection: 480 mcg/1.6 mL in a single-dose vial (3)

Prefilled Syringe
- Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe (3)
- Injection: 480 mcg/0.8 mL in a single-dose prefilled syringe (3)

---------- CONTRAINDICATIONS ----------
Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim products or pegfilgrastim products. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS.
- Discontinue NIVESTYM in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue NIVESTYM in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of NIVESTYM if causality is likely. (5.5)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions in patients:
- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea. (6.1)
- With AML (≥ 2% difference in incidence) are pain, epistaxis and rash. (6.1)
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash. (6.1)
- Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia and headache. (6.1)
- With severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of NIVESTYM has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 7/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 1.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy
- 1.3 Patients with Cancer Undergoing Bone Marrow Transplantation
- 1.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
- 1.5 Patients with Severe Chronic Neutropenia

2 DOSAGE AND ADMINISTRATION
- 2.1 Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML
- 2.2 Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation
- 2.3 Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

NIVESTYM is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever *[see Clinical Studies (14.1)]*.

1.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

NIVESTYM is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) *[see Clinical Studies (14.2)]*.

1.3 Patients with Cancer Undergoing Bone Marrow Transplantation

NIVESTYM is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation *[see Clinical Studies (14.3)]*.

1.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

NIVESTYM is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis *[see Clinical Studies (14.4)]*.

1.5 Patients with Severe Chronic Neutropenia

NIVESTYM is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia *[see Clinical Studies (14.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML

The recommended starting dosage of NIVESTYM is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting NIVESTYM therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping NIVESTYM if the ANC increases beyond 10,000/mm^3 *[see Warnings and Precautions (5.10)]*.

Administer NIVESTYM at least 24 hours after cytotoxic chemotherapy. Do not administer NIVESTYM within the 24-hour period prior to chemotherapy *[see Warnings and Precautions (5.13)]*. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of NIVESTYM therapy. Therefore, to ensure a sustained therapeutic response, administer NIVESTYM daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of NIVESTYM therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

2.2 Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation

The recommended dosage of NIVESTYM following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. Administer the first dose of NIVESTYM at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of NIVESTYM against the neutrophil response (see Table 1).

Table 1. Recommended Dosage Adjustments During Neutrophil Recovery in Patients with Cancer Following BMT

Absolute Neutrophil Count	NIVESTYM Dosage Adjustment
When ANC greater than 1000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
Then, if ANC remains greater than 1000/mm^3 for 3 more consecutive days	Discontinue NIVESTYM
Then, if ANC decreases to less than 1000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase NIVESTYM to 10 mcg/kg/day, and then follow the above steps.

2.3 Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The recommended dosage of NIVESTYM for the mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer NIVESTYM for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of NIVESTYM administration and leukapheresis schedule have not been established, administration of filgrastim for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective *[see Clinical Studies (14.4)]*. Monitor neutrophil counts after 4 days of NIVESTYM, and discontinue NIVESTYM if the white blood cell (WBC) count rises to greater than 100,000/mm^3.

2.4 Dosage in Patients with Severe Chronic Neutropenia

Prior to starting NIVESTYM in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of NIVESTYM prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommended starting dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection.

Dosage Adjustments in Patients with Severe Chronic Neutropenia

Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN postmarketing surveillance study, the reported median daily doses of filgrastim were: 6 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of filgrastim greater than or equal to 100 mcg/kg/day.

Monitor CBCs for Dosage Adjustments

During the initial 4 weeks of NIVESTYM therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended.

2.5 Important Administration Instructions

Patient self-administration and administration by a caregiver may benefit from training by a healthcare professional. Training should aim to demonstrate to those patients and caregivers how to measure the dose using the prefilled syringe, and the focus should be on ensuring that a patient or caregiver can successfully perform all of the steps in the Instructions for Use of NIVESTYM prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of NIVESTYM *[see Instructions for Use]*.

NIVESTYM prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of NIVESTYM less than 0.3 mL (180 mcg) for direct administration. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use NIVESTYM single-dose vial.

NIVESTYM is supplied in single-dose vials (for subcutaneous use or intravenous infusion) and single-dose prefilled syringes (for subcutaneous use) *[see Dosage Forms and Strengths (3)]*. Prior to use, remove the vial or prefilled syringe from the refrigerator and allow NIVESTYM to reach room temperature for a minimum of 30 minutes and a maximum of 24 hours. Discard any vial or prefilled syringe left at room temperature for greater than 24 hours. Visually inspect NIVESTYM for particulate matter and discoloration prior to administration (the solution is clear and colorless). Do not administer NIVESTYM if particulates or discoloration are observed.

Discard unused portion of NIVESTYM in vials or prefilled syringes; do not re-enter the vial. Do not save unused drug for later administration.

Subcutaneous Injection

Inject NIVESTYM subcutaneously in the outer area of upper arms, abdomen, thighs, or upper outer areas of the buttock. If patients or caregivers are to administer NIVESTYM, instruct them in appropriate injection technique and ask them to follow the subcutaneous injection procedures in the Instructions for Use for the vial or prefilled syringe *[see Patient Counseling Information (17)]*.

Training by the healthcare provider should aim to demonstrate to those patients and caregivers how to measure the dose of NIVESTYM, and the focus should be on ensuring that a patient or caregiver can successfully perform all of the steps in the Instructions for Use for the vial or prefilled syringe. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of NIVESTYM or whether the patient would benefit from a different NIVESTYM presentation. If a patient or caregiver experiences difficulty measuring the required dose, especially if it is other than the entire contents of the NIVESTYM prefilled syringe, use of the NIVESTYM vial may be considered.

If the patient or caregiver misses a dose of NIVESTYM, instruct them to contact their healthcare provider.

Administration Instructions for the Prefilled Syringe
The NIVESTYM syringe plunger stopper and needle cover are not made with natural rubber latex.

Administration Instructions for Dilution (Vial Only)
If required for intravenous administration, NIVESTYM (vial only) may be diluted in 5% Dextrose Injection, USP from a concentration of 300 mcg/mL to 5 mcg/mL (do not dilute to a final concentration less than 5 mcg/mL). NIVESTYM diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% Dextrose Injection, USP or 5% Dextrose plus Albumin (Human), NIVESTYM is compatible with glass bottles, polyvinyl chloride (PVC) and polyolefin intravenous bags, and polypropylene syringes. **Do not dilute with saline at any time because the product may precipitate.**

Diluted NIVESTYM solution can be stored at room temperature for up to 24 hours. This 24 hour time period includes the time during room temperature storage of the infusion solution and the duration of the infusion.

3 DOSAGE FORMS AND STRENGTHS

Vial:
- Injection: 300 mcg/mL of a clear, colorless solution in a single-dose vial
- Injection: 480 mcg/1.6 mL of a clear, colorless solution in a single-dose vial

Prefilled Syringe:
- Injection: 300 mcg/0.5 mL of a clear, colorless solution in a single-dose prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard
- Injection: 480 mcg/0.8 mL of a clear, colorless solution in a single-dose prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard

4 CONTRAINDICATIONS

NIVESTYM is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim products or pegfilgrastim products *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Splenic Rupture
Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome
Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue NIVESTYM in patients with ARDS.

5.3 Serious Allergic Reactions
Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim products. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving filgrastim products can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue NIVESTYM in patients with serious allergic reactions. NIVESTYM is

contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim.

5.4 Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim products. Discontinue NIVESTYM if sickle cell crisis occurs.

5.5 Glomerulonephritis

Glomerulonephritis has occurred in patients receiving filgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of filgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of NIVESTYM.

5.6 Alveolar Hemorrhage and Hemoptysis

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors treated with filgrastim products for peripheral blood progenitor cell (PBPC) \ mobilization. Hemoptysis resolved with discontinuation of filgrastim products. The use of NIVESTYM for PBPC mobilization in healthy donors is not an approved indication.

5.7 Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after G-CSF administration, including filgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

5.8 Patients with Severe Chronic Neutropenia

Confirm the diagnosis of SCN before initiating NIVESTYM therapy. Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with filgrastim products for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of filgrastim products on the development of abnormal cytogenetics and the effect of continued filgrastim products administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing NIVESTYM should be carefully considered.

5.9 Thrombocytopenia

Thrombocytopenia has been reported in patients receiving filgrastim products. Monitor platelet counts.

5.10 Leukocytosis

Patients with Cancer Receiving Myelosuppressive Chemotherapy

White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving filgrastim at dosages above 5 mcg/kg/day. In patients with cancer receiving NIVESTYM as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that NIVESTYM therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy. Dosages of NIVESTYM that increase the ANC beyond 10,000/mm^3 may

not result in any additional clinical benefit. In patients with cancer receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Peripheral Blood Progenitor Cell Collection and Therapy
During the period of administration of NIVESTYM for PBPC mobilization in patients with cancer, discontinue NIVESTYM if the leukocyte count rises to > 100,000/mm^3.

5.11 Cutaneous Vasculitis
Cutaneous vasculitis has been reported in patients treated with filgrastim products. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Hold NIVESTYM therapy in patients with cutaneous vasculitis. NIVESTYM may be started at a reduced dose when the symptoms resolve and the ANC has decreased.

5.12 Potential Effect on Malignant Cells
NIVESTYM is a growth factor that primarily stimulates neutrophils. The granulocyte-colony-stimulating factor (G-CSF) receptor through which NIVESTYM acts has also been found on tumor cell lines. The possibility that NIVESTYM acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim products in chronic myeloid leukemia (CML) and myelodysplasia has not been established.

When NIVESTYM is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells has not been well studied, and the limited data available are inconclusive.

5.13 Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended
The safety and efficacy of NIVESTYM given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use NIVESTYM in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy *[see Dosage and Administration (2.2)]*.

The safety and efficacy of NIVESTYM have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of NIVESTYM with chemotherapy and radiation therapy.

5.14 Nuclear Imaging
Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

5.15 Aortitis
Aortitis has been reported in patients receiving filgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue NIVESTYM if aortitis is suspected.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture *[see Warnings and Precautions (5.1)]*
- Acute Respiratory Distress Syndrome *[see Warnings and Precautions (5.2)]*
- Serious Allergic Reactions *[see Warnings and Precautions (5.3)]*
- Sickle Cell Disorders *[see Warnings and Precautions (5.4)]*
- Glomerulonephritis *[see Warnings and Precautions (5.5)]*
- Alveolar Hemorrhage and Hemoptysis *[see Warnings and Precautions (5.6)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.7)]*
- Thrombocytopenia *[see Warnings and Precautions (5.9)]*
- Leukocytosis *[see Warnings and Precautions (5.10)]*
- Cutaneous Vasculitis *[see Warnings and Precautions (5.11)]*
- Aortitis *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy

The following adverse reaction data in Table 2 are from three randomized, placebo-controlled studies in patients with:

- small cell lung cancer receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide (Study 1)
- small cell lung cancer receiving ifosfamide, doxorubicin, and etoposide (Study 2), and
- non-Hodgkin's lymphoma (NHL) receiving doxorubicin, cyclophosphamide, vindesine, bleomycin, methylprednisolone, and methotrexate ("ACVBP") or mitoxantrone, ifosfamide, mitoguazone, teniposide, methotrexate, folinic acid, methylprednisolone, and methotrexate ("VIM3") (Study 3).

A total of 451 patients were randomized to receive subcutaneous filgrastim 230 mcg/m^2 (Study 1), 240 mcg/m^2 (Study 2) or 4 or 5 mcg/kg/day (Study 3) (n = 294) or placebo (n = 157). The patients in these studies were median age 61 (range 29 to 78) years and 64% were male. The ethnicity was 95% Caucasian, 4% African American, and 1% Asian.

Table 2. Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy (With ≥ 5% Higher Incidence in Filgrastim Compared to Placebo)

System Organ Class Preferred Term	Filgrastim (N = 294)	Placebo (N = 157)
Blood and lymphatic system disorders		
Thrombocytopenia	38%	29%
Gastrointestinal disorders		
Nausea	43%	32%
General disorders and administration site conditions		
Pyrexia	48%	29%
Chest pain	13%	6%
Pain	12%	6%
Fatigue	20%	10%
Musculoskeletal and connective tissue disorders		
Back pain	15%	8%
Arthralgia	9%	2%
Bone pain	11%	6%
Pain in extremity*	7%	3%
Nervous system disorders		
Dizziness	14%	3%
Respiratory, thoracic and mediastinal disorders		
Cough	14%	8%
Dyspnea	13%	8%
Skin and subcutaneous tissue disorders		
Rash	14%	5%
Investigations		
Blood lactate dehydrogenase increased	6%	1%
Blood alkaline phosphatase increased	6%	1%

* Percent difference (Filgrastim – Placebo) was 4%.

Adverse events with ≥ 5% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy delivered included anemia, constipation, diarrhea, oral pain, vomiting, asthenia, malaise, edema peripheral, hemoglobin decreased, decreased appetite, oropharyngeal pain, and alopecia.

Adverse Reactions in Patients with Acute Myeloid Leukemia

Adverse reaction data below are from a randomized, double-blind, placebo-controlled study in patients with AML (Study 4) who received an induction chemotherapy regimen of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5 and up to 3 additional courses of therapy (induction 2, and consolidation 1, 2) of intravenous daunorubicin, cytosine arabinoside, and etoposide. The safety population included 518 patients randomized to receive either 5 mcg/kg/day filgrastim (n = 257) or placebo (n = 261). The median age was 54 (range 16 to 89) years and 54% were male.

Adverse reactions with ≥ 2% higher incidence in filgrastim patients compared to placebo included epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular.

Adverse events with ≥ 2% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy included diarrhea, constipation, and transfusion reaction.

Adverse Reactions in Patients with Cancer Undergoing Bone Marrow Transplantation

The following adverse reaction data are from one randomized, no treatment-controlled study in patients with acute lymphoblastic leukemia or lymphoblastic lymphoma receiving high-dose chemotherapy (cyclophosphamide or cytarabine, and melphalan) and total body irradiation (Study 5) and one randomized, no treatment controlled study in patients with Hodgkin's disease

(HD) and NHL undergoing high-dose chemotherapy and autologous bone marrow transplantation (Study 6). Patients receiving autologous bone marrow transplantation only were included in the analysis. A total of 100 patients received either 30 mcg/kg/day as a 4 hour infusion (Study 5) or 10 mcg/kg/day or 30 mcg/kg/day as a 24 hour infusion (Study 6) filgrastim (n = 72), no treatment control or placebo (n = 28). The median age was 30 (range 15 to 57) years, 57% were male.

Adverse reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included rash and hypersensitivity.

Adverse reactions in patients receiving intensive chemotherapy followed by autologous BMT with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia.

Adverse Reactions in Patients with Cancer Undergoing Autologous Peripheral Blood Progenitor Cell Collection

The adverse reaction data in Table 3 are from a series of 7 trials in patients with cancer undergoing mobilization of autologous peripheral blood progenitor cells for collection by leukapheresis. Patients (n = 166) in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 8 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dosage of filgrastim ranged between 5 to 30 mcg/kg/day and was administered subcutaneously by injection or continuous infusion. The median age was 39 (range 15 to 67) years, and 48% were male.

Table 3. Adverse Reactions in Patients with Cancer Undergoing Autologous PBPC in the Mobilization Phase (≥ 5% Incidence in Filgrastim Patients)

System Organ Class Preferred Term	Mobilization Phase (N = 166)
Musculoskeletal and connective tissue disorders	
Bone pain	30%
General disorders and administration site conditions	
Pyrexia	16%
Investigations	
Blood alkaline phosphatase increased	11%
Nervous system disorders	
Headache	10%

Adverse Reactions in Patients with Severe Chronic Neutropenia

The following adverse reaction data were identified in a randomized, controlled study in patients with SCN receiving filgrastim (Study 7). 123 patients were randomized to a 4 month observation period followed by subcutaneous filgrastim treatment or immediate subcutaneous filgrastim treatment. The median age was 12 years (range 7 months to 76 years) and 46% were male. The dosage of filgrastim was determined by the category of neutropenia. Initial dosage of filgrastim:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dosage was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

Adverse reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, and urinary tract infection (upper respiratory tract infection and urinary tract infection were higher in the filgrastim arm, total

infection related events were lower in filgrastim treated patients), epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to filgrastim in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The incidence of antibody development in patients receiving filgrastim products has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim products, the nature and specificity of these antibodies has not been adequately studied. In clinical studies using filgrastim, the incidence of antibodies binding to filgrastim was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell-based bioassay.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of filgrastim products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions (5.1)]*
- acute respiratory distress syndrome *[see Warnings and Precautions (5.2)]*
- anaphylaxis *[see Warnings and Precautions (5.3)]*
- sickle cell disorders *[see Warnings and Precautions (5.4)]*
- glomerulonephritis *[see Warnings and Precautions (5.5)]*
- alveolar hemorrhage and hemoptysis *[see Warnings and Precautions (5.6)]*
- capillary leak syndrome *[see Warnings and Precautions (5.7)]*
- leukocytosis *[see Warnings and Precautions (5.10)]*
- cutaneous vasculitis *[see Warnings and Precautions (5.11)]*
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- decreased bone density and osteoporosis in pediatric patients receiving chronic treatment with filgrastim products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled clinical studies in pregnant women, therefore the potential risk to the fetus with the use of filgrastim products is unknown. Reports in the scientific literature have described transplacental passage of filgrastim in pregnant women when administered ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation). In animal reproduction studies, effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations

were observed in either species. No maternal or fetal effects were observed in pregnant rats at doses up to 58 times the human doses. Filgrastim been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Human data

Several observational studies based on the Severe Chronic Neutropenia International Registry (SCNIR) described pregnancy outcomes in women with severe chronic neutropenia (SCN) who were exposed to filgrastim products during pregnancy and women with SCN who were unexposed. No major differences were seen between treated and untreated women with respect to pregnancy outcome (including miscarriage and preterm labor), newborn complications (including birth weight) and infections. Methodological limitations of these studies, include small sample size, and lack of generalizability due to the underlying maternal condition.

Animal data
Effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations were observed in either species. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses. In pregnant rabbits showing signs of maternal toxicity, reduced embryo-fetal survival (at 20 and 80 mcg/kg/day) and increased abortions (at 80 mcg/kg/day) were observed. In pregnant rats, no maternal or fetal effects were observed at doses up to 575 mcg/kg/day, which is approximately 58 times higher than the human dose of 10 mcg/kg/day.

Offspring of rats administered filgrastim during the peri-natal and lactation periods exhibited a delay in external differentiation and growth retardation (≥ 20 mcg/kg/day) and slightly reduced survival rate (100 mcg/kg/day).

8.2 Lactation

Risk Summary

There is published literature documenting transfer of filgrastim products into human milk. There are a few case reports describing the use of filgrastim products in breastfeeding mothers with no adverse effects noted in the infants. There are no data on the effects of filgrastim products on milk production. Other recombinant filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NIVESTYM and any potential adverse effects on the breastfed child from NIVESTYM or from the underlying maternal condition.

8.4 Pediatric Use

NIVESTYM prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard may not accurately measure volumes less than 0.3 mL due to the needle spring mechanism design. Therefore, the direct administration of a volume less than 0.3 mL using NIVESTYM prefilled syringe is not recommended due to the potential for dosing errors. For direct administration of doses less than 0.3 mL (180 mcg) use NIVESTYM single-dose vial.

In patients with cancer receiving myelosuppressive chemotherapy, 15 pediatric patients median age 2.6 (range 1.2 to 9.4) years with neuroblastoma were treated with myelosuppressive chemotherapy (cyclophosphamide, cisplatin, doxorubicin, and etoposide) followed by subcutaneous filgrastim at doses of 5, 10, or 15 mcg/kg/day for 10 days (n = 5/dose) (Study 8). The pharmacokinetics of filgrastim in pediatric patients after chemotherapy were similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim. In this population, filgrastim was well-tolerated. There was one report of palpable splenomegaly and one report of hepatosplenomegaly associated with filgrastim therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

The safety and effectiveness of filgrastim have been established in pediatric patients with SCN *[see Clinical Studies (14.5)]*. In a phase 3 study (Study 7) to assess the safety and efficacy of filgrastim in the treatment of SCN, 123 patients with a median age of 12 years (range 7 months to 76 years) were studied. Of the 123 patients, 12 were infants (7 months to 2 years of age), 49 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 731 patients in the surveillance study, 429 were pediatric patients < 18 years of age (range 0.9 to 17) *[see Indications and Usage (1.5), Dosage and Administration (2.5), and Clinical Studies (14.5)]*.

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of filgrastim treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown *[see Warnings and Precautions (5.8) and Adverse Reactions (6)]*.

8.5 Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo-controlled trials of filgrastim-treated patients receiving myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Clinical studies of filgrastim in other approved indications (i.e., BMT recipients, PBPC mobilization, and SCN) did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects.

10 OVERDOSAGE

The maximum tolerated dose of filgrastim products has not been determined. In filgrastim clinical trials of patients with cancer receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

11 DESCRIPTION

Filgrastim-aafi is a 175 amino acid human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology.

NIVESTYM is produced by *Escherichia coli* (*E coli)* bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. NIVESTYM has a molecular weight of 18,799 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E coli*. Because NIVESTYM is produced in *E coli*, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

NIVESTYMis a sterile, clear, colorless, preservative-free liquid containing filgrastim-aafi injection for subcutaneous or intravenous use. The product is available in single-dose vials and prefilled syringes. The single-dose vials contain either 300 mcg/mL or 480 mcg/1.6 mL of filgrastim-aafi. The single-dose prefilled syringes contain either 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim-aafi. See Table 4 below for product composition of each single-dose vial or prefilled syringe.

Table 4. Product Composition

	300mcg/mL Vial	**480 mcg/1.6 mL Vial**	**300 mcg/0.5 mL Syringe**	**480 mcg/0.8 mL Syringe**
Filgrastim-aafi	300 mcg	480 mcg	300 mcg	480 mcg
Acetate Polysorbate 80 Sodium Sorbitol Water for Injection USP q.s. ad*	0.59 mg 0.04 mg 0.035 mg 50 mg 1 mL	0.94 mg 0.064 mg 0.056 mg 80 mg 1.6 mL	0.295 mg 0.02 mg 0.0175 mg 25 mg 0.5 mL	0.472 mg 0.032 mg 0.028 mg 40 mg 0.8 mL

* quantity sufficient to make

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

Endogenous G-CSF is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production or activity of hematopoietic cell types other than the neutrophil lineage.

12.2 Pharmacodynamics

In phase 1 studies involving 96 patients with various non-myeloid malignancies, filgrastim administration resulted in a dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 mcg/kg/day. This increase in neutrophil counts was observed whether filgrastim

was administered intravenous (1 to 70 mcg/kg twice daily), subcutaneous (1 to 3 mcg/kg once daily), or by continuous subcutaneous infusion (3 to 11 mcg/kg/day). With discontinuation of filgrastim therapy, neutrophil counts returned to baseline in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic (measured by migration under agarose using N-formyl-methionyl-leucyl-phenylalanine [fMLP] as the chemotaxin) activity in vitro.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving filgrastim; however, the percentage of monocytes in the differential count remained within the normal range. Absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of filgrastim. Increases in lymphocyte counts following filgrastim administration have been reported in some normal subjects and patients with cancer.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, Dohle bodies, increased granulocyte granulation, and hypersegmented neutrophils have been observed. Such changes were transient and were not associated with clinical sequelae, nor were they necessarily associated with infection.

12.3 Pharmacokinetics

Filgrastim products exhibit nonlinear pharmacokinetics. Clearance is dependent on filgrastim product concentration and neutrophil count: G-CSF receptor-mediated clearance is saturated by high concentration of filgrastim products and is diminished by neutropenia. In addition, filgrastim products are cleared by the kidney.

Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg of filgrastim resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. After intravenous administration, the volume of distribution averaged 150 mL/kg and the elimination half-life was approximately 3.5 hours in both normal subjects and cancer subjects. Clearance rates of filgrastim were approximately 0.5 to 0.7 mL/minute/kg. Single parenteral doses or daily intravenous doses, over a 14-day period, resulted in comparable half-lives. The half-lives were similar for intravenous administration (231 minutes, following doses of 34.5 mcg/kg) and for subcutaneous administration (210 minutes, following filgrastim dosages of 3.45 mcg/kg). Continuous 24-hour intravenous infusions of 20 mcg/kg over an 11 to 20-day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated. The absolute bioavailability of filgrastim after subcutaneous administration is 60% to 70%.

Specific Populations

Pediatric Patients

The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adult patients receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim *[see Use in Specific Populations (8.4)]*.

Renal Impairment

In a study with healthy volunteers, subjects with moderate renal impairment, and subjects with end-stage renal disease (n = 4 per group), higher serum concentrations were observed in subjects with end-stage renal disease. However, dose adjustment in patients with renal impairment is not necessary.

Hepatic Impairment

Pharmacokinetics and pharmacodynamics of filgrastim are similar between subjects with hepatic impairment and healthy subjects (n = 12/group). The study included 10 subjects with mild hepatic impairment (Child-Pugh Class A) and 2 subjects with moderate hepatic impairment (Child-Pugh Class B). Therefore, NIVESTYM dose adjustment for in patients with hepatic impairment is not necessary.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of filgrastim products has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. Filgrastim had no observed effect on the fertility of male or female rats at doses up to 500 mcg/kg.

13.2 Animal Toxicology and Pharmacology

Filgrastim was administered to monkeys, dogs, hamsters, rats, and mice as part of a nonclinical toxicology program, which included studies up to 1 year duration. In the repeated-dose studies, changes observed were attributable to the expected pharmacological actions of filgrastim (i.e., dose-dependent increases in white blood cell counts, increased circulating segmented neutrophils, and increased myeloid:erythroid ratio in bone marrow). Histopathologic examination of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis, and dose-related increases in spleen weight were seen in all species. These changes all reversed after discontinuation of treatment.

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The safety and efficacy of filgrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive filgrastim (n = 99) at a dose of 230 mcg/m^2 (4 to 8 mcg/kg/day) or placebo (n = 111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease.

The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC < 1000/mm^3 and temperature > 38.2°C. Treatment with filgrastim resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for filgrastim -treated patients and 76% for placebo-treated patients ($p < 0.001$). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm^3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

14.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of filgrastim to reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid

leukemia (AML) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, de novo AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous filgrastim (n = 259) at a dose of 5 mcg/kg/day or placebo (n = 262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC $\geq$ 1000/mm^3 for 3 consecutive days or $\geq$ 10,000/mm^3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white blood cell count (65% < 25,000/mm^3 and 27% > 100,000/mm^3); 29% unfavorable cytogenetics.

The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm^3. Treatment with filgrastim resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, filgrastim -treated patients 14 days, placebo-treated patients 19 days (p = 0.0001: difference of 5 days (95% CI: -6.0, -4.0)).

There was a reduction in the median duration of intravenous antibiotic use, filgrastim -treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, filgrastim-treated patients: 20 days versus placebo-treated patients: 25 days.

There were no statistically significant differences between the filgrastim and the placebo groups in complete remission rate (69% - filgrastim, 68% - placebo), median time to progression of all randomized patients (165 days - filgrastim, 186 days - placebo), or median overall survival (380 days - filgrastim, 425 days - placebo).

14.3 Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo controlled trial (Study 10).

In Study 6 patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, filgrastim 10 mcg/kg/day, and filgrastim 30 mcg/kg/day as a 24 hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's disease and 31% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm^3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) occurred in the filgrastim -treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, p = 0.004]).

In Study 9, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion filgrastim 10 mcg/kg/day (n = 19), filgrastim 30 mcg/kg/day (n = 10) and no treatment (n = 14) starting the day after marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia ($ANC < 500/mm^3$) in the filgrastim-treated groups versus the control group (21.5 days in the control group versus 10 days in the filgrastim -treated groups, $p < 0.001$). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the filgrastim--treated groups, $p < 0.0001$).

In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive filgrastim 300 mcg/m^2/day (n = 33) or placebo (n = 37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, $p < 0.001$) and time to recovery of ANC to $\geq 500/mm^3$ (21 days in the control group and 16 days in the treatment group, $p < 0.001$).

14.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The safety and efficacy of filgrastim to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using filgrastim mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of filgrastim ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using filgrastim mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count $\geq 20{,}000/mm^3$ by day 28. In clinical trials of filgrastim for the mobilization of hematopoietic progenitor cells, filgrastim was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC ($\geq 500/mm^3$) was reached. The rate of engraftment of these cells in the absence of filgrastim post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received filgrastim-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). Patients received daily filgrastim 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin's disease and 43% non-Hodgkin's lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to filgrastim-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

14.5 Patients with Severe Chronic Neutropenia

The safety and efficacy of filgrastim to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with severe neutropenia (Study 7).

Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm^3 on three occasions during a 6 month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm^3 per cycle. In addition, patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4 month observation period followed by filgrastim treatment or immediate filgrastim treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia.

Filgrastim was administered subcutaneously. The dose of filgrastim was determined by the category of neutropenia. Initial dose of filgrastim:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

The main efficacy endpoint was response to filgrastim treatment. ANC response from baseline (< 500/mm^3) was defined as follows:

- Complete response: median ANC > 1500/mm^3
- Partial response: median ANC ≥ 500/mm^3 and ≤ 1500/mm^3 with a minimum increase of 100%
- No response: median ANC < 500/mm^3

There were 112 of 123 patients who demonstrated a complete or partial response to filgrastim treatment.

Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving filgrastim of the following parameters:

- incidence of infection
- incidence of fever
- duration of fever
- incidence, duration, and severity of oropharyngeal ulcers
- number of days of antibiotic use

The incidence for each of these 5 clinical parameters was lower in the filgrastim arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although filgrastim substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vials

Injection: Single-dose vials containing 300 mcg/mL of a sterile, clear, colorless, preservative-free filgrastim-aafi solution. Dispensing packs of 10 vials (NDC 0069-0293-10).

Injection: Single-dose vials containing 480 mcg/1.6 mL (300 mcg/mL) of a sterile, clear, colorless, preservative-free filgrastim-aafi solution. Dispensing packs of 10 vials (NDC 0069-0294-10).

Prefilled Syringes
Injection: Single-dose prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard, containing 300 mcg/0.5 mL of a sterile, clear, colorless, preservative-free filgrastim-aafi solution.

- Pack of 1 prefilled syringe (NDC 0069-0291-01).
- Pack of 10 prefilled syringes (NDC 0069-0291-10).

Injection: Single-dose, prefilled syringe with BD UltraSafe Plus™ Passive Needle Guard, containing 480 mcg/0.8 mL of a sterile, clear, colorless, preservative-free filgrastim-aafi solution.

- Pack of 1 prefilled syringe (NDC 0069-0292-01).
- Pack of 10 prefilled syringes (NDC 0069-0292-10).

The NIVESTYM syringe plunger stopper and needle cover are not made with natural rubber latex *[see Dosage and Administration (2.5)]*.

Storage
Store NIVESTYM in the refrigerator at 2° to 8°C (36° to 46°F) in the original carton to protect from light. Do not leave NIVESTYM in direct sunlight. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard NIVESTYM if frozen more than once. Avoid shaking. Transport via a pneumatic tube has not been studied.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). Review the steps for direct patient administration with patients and caregivers. Training by the healthcare provider should aim to ensure that patients and caregivers can successfully perform all of the steps in the Instructions for Use of NIVESTYM vial and prefilled syringe, including showing the patient or caregiver how to measure the required dose, particularly if a patient is on a dose other than the entire prefilled syringe. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of NIVESTYM or whether the patient would benefit from a different NIVESTYM presentation. Advise patients of the following risks and potential risks with NIVESTYM:

- Rupture or enlargement of the spleen may occur. Symptoms include left upper quadrant abdominal pain or left shoulder pain. Advise patients to report pain in these areas to their physician immediately *[see Warnings and Precautions (5.1)]*.
- Dyspnea, with or without fever, progressing to Acute Respiratory Distress Syndrome, may occur.
  Advise patients to report dyspnea to their physician immediately *[see Warnings and Precautions (5.2)]*.
- Serious allergic reactions may occur, which may be signaled by rash, facial edema, wheezing, dyspnea, hypotension, or tachycardia. Advise patients to seek immediate medical attention if signs or symptoms of hypersensitivity reaction occur *[see Warnings and Precautions (5.3)]*.
- In patients with sickle cell disease, sickle cell crisis and death have occurred. Discuss potential risks and benefits for patients with sickle cell disease prior to the administration of human granulocyte colony-stimulating factors *[see Warnings and Precautions (5.4)]*.
- Glomerulonephritis may occur. Symptoms include swelling of the face or ankles, dark colored urine or blood in the urine, or a decrease in urine production. Advise patients to report signs or symptoms of glomerulonephritis to their physician immediately *[see Warnings and Precautions (5.5)]*.

- Cutaneous vasculitis may occur, which may be signaled by purpura or erythema. Advise patients to report signs or symptoms of vasculitis to their physician immediately *[see Warnings and Precautions (5.11)]*.
- Aortitis may occur. Symptoms may include fever, abdominal pain, malaise, back pain, and increase inflammatory markers. Advise patients to report signs and symptoms of aortitis to their physician immediately *[see Warnings and Precautions (5.15)]*.

Instruct patients who self-administer NIVESTYM using the prefilled syringe or single-dose vial of the:

- Importance of following the applicable Instructions for Use.
- Dangers of reusing needles, syringes, or unused portions of single-dose vials.
- Importance of following local requirements for proper disposal of used syringes, needles, and unused vials.
- Importance of informing the healthcare provider if difficulty occurs when measuring or administering partial contents of the NIVESTYM prefilled syringe. If difficulty occurs, use of the NIVESTYM vial may be considered.
- Difference in product concentration of the NIVESTYM prefilled syringe in comparison to the NIVESTYM vial. When switching patients from the NIVESTYM prefilled syringe to the NIVESTYM vial, or vice versa, ensure that patients understand the correct volume to be administered since the concentration of NIVESTYM differs between the prefilled syringe and the vial.

This product's label may have been updated. For full prescribing information, please visit www.pfizer.com.

Manufactured by:
Hospira, Inc.,
a Pfizer Company
Lake Forest, IL 60045 USA
US License No. 1974

LAB-0933-0.3

Patient Information
NIVESTYM (**Neye-ves-tim**)
(filgrastim-aafi)
injection

What is NIVESTYM?
NIVESTYM is a man-made form of granulocyte colony-stimulating factor (G-CSF). G-CSF is a substance produced by the body. It stimulates the growth of neutrophils, a type of white blood cell important in the body's fight against infection.

Do not take NIVESTYM if you have had a serious allergic reaction to human G-CSFs such as filgrastim products or pegfilgrastim products.

Before you take NIVESTYM, tell your healthcare provider about all of your medical conditions, including if you:

- have a sickle cell disorder.
- have kidney problems.
- are receiving radiation therapy.
- are pregnant or plan to become pregnant. It is not known if NIVESTYM will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if NIVESTYM passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive NIVESTYM?

- **NIVESTYM injections can be given by a healthcare provider by intravenous (IV) infusion or under your skin (subcutaneous injection). Your healthcare provider may decide subcutaneous injections can be given at home by you or your caregiver. If NIVESTYM is given at home, see the detailed "Instructions for Use" that comes with your NIVESTYM for information on how to prepare and inject a dose of NIVESTYM.**
- You and your caregiver should be shown how to prepare and inject NIVESTYM before you use it, by your healthcare provider.
- You should not try to inject a dose of NIVESTYM less than 0.3 mL (180 mcg) from a NIVESTYM prefilled syringe. A dose less than 0.3 mL cannot be accurately measured using the NIVESTYM prefilled syringe.
- Your healthcare provider will tell you how much NIVESTYM to inject and when to inject it. Do not change your dose or stop NIVESTYM unless your healthcare provider tells you to.
- If you are receiving NIVESTYM because you are also receiving chemotherapy, your dose of NIVESTYM should be injected at least 24 hours before or 24 hours after your dose of chemotherapy.
- If you miss a dose of NIVESTYM, talk to your healthcare provider about when you should give your next dose.

What are the possible side effects of NIVESTYM?
NIVESTYM may cause serious side effects, including:

- **Spleen rupture.** Your spleen may become enlarged and can rupture. A ruptured spleen can cause death. Call your healthcare provider right away if you have pain in the left upper stomach (abdomen) area or your left shoulder.
- **A serious lung problem called acute respiratory distress syndrome (ARDS).** Call your healthcare provider or get emergency medical help right away if you have shortness of breath with or without a fever, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.** NIVESTYM can cause serious allergic reactions. These reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness, swelling around your mouth or eyes, fast heart rate, and sweating. If you have any of these symptoms, stop using NIVESTYM and call your healthcare provider or get emergency medical help right away.
- **Sickle cell crises.** You may have a serious sickle cell crisis if you have a sickle cell disorder and receive NIVESTYM. Serious sickle cell crises have happened in people with sickle cell disorders receiving filgrastim that has sometimes led to death. Call your healthcare provider right away if you have symptoms of sickle cell crisis such as pain or

difficulty breathing.

- **Kidney injury (glomerulonephritis).** NIVESTYM can cause kidney injury. Call your healthcare provider right away if you develop any of the following symptoms:
  - swelling of your face or ankles
  - blood in your urine or dark colored urine
  - you urinate less than usual
- **Capillary leak syndrome.** NIVESTYM can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
  - swelling or puffiness and are urinating less than usual
  - trouble breathing
  - swelling of your stomach-area (abdomen) and feeling of fullness
  - dizziness or feeling faint
  - a general feeling of tiredness
- **Decreased platelet count (thrombocytopenia).** Your healthcare provider will check your blood during treatment with NIVESTYM. Tell your healthcare provider if you have unusual bleeding or bruising during treatment with NIVESTYM. This could be a sign of decreased platelet counts, which may reduce the ability of your blood to clot.
- **Increased white blood cell count (leukocytosis).** Your healthcare provider will check your blood during treatment with NIVESTYM.
- **Inflammation of your blood vessels (cutaneous vasculitis).** Tell your healthcare provider if you develop purple spots or redness of your skin.
- **Inflammation of the aorta (aortitis).** Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) may be caused by NIVESTYM. Symptoms may include fever, abdominal pain, feeling tired, and back pain. Call your healthcare provider if you experience these symptoms.

The most common side effects of NIVESTYM include aching in the bones and muscles. These are not all the possible side effects of NIVESTYM. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NIVESTYM?

- Store NIVESTYM in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze.
- Keep NIVESTYM in the original carton to protect from light or physical damage.
- Do not shake NIVESTYM.
- Take NIVESTYM out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- Throw away (dispose of) any NIVESTYM that has been left at room temperature for longer than 24 hours.
- After you inject your dose, throw away (dispose of) any unused NIVESTYM left in the vials or prefilled syringes. Do not save unused NIVESTYM in the vials or prefilled syringes for later use.

Keep NIVESTYM out of the reach of children.

General information about the safe and effective use of NIVESTYM.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NIVESTYM for a condition for which it was not prescribed. Do not give NIVESTYM to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about NIVESTYM that is written for healthcare professionals.

What are the ingredients in NIVESTYM?

Active ingredient: (filgrastim-aafi)

Inactive ingredients: acetate, polysorbate 80, sodium, sorbitol, and water for Injection

Manufactured by Hospira, Inc., a Pfizer Company, Lake Forest, IL 60045 USA
US License No. 1974

LAB-0935-0.2
For more information go to www.pfizer.com or call 1-800-438-1985.

Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 7/2018

Instructions for Use
NIVESTYM (Neye-ves-tim)
(filgrastim-aafi)
injection
Single-Dose Prefilled Syringe

Important

Read the Patient Information for important information you need to know about NIVESTYM before using this Instructions for Use.

Before you use a NIVESTYM prefilled syringe, read this important information.

Storing your prefilled syringe

- Store the NIVESTYM prefilled syringe in the refrigerator between 36˚F to 46˚F (2˚C to 8˚C).
- **Do not freeze.**
- Keep the NIVESTYM prefilled syringe in the original carton to protect from light or physical damage.
- Take the prefilled syringe out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- The NIVESTYM prefilled syringe may be allowed to reach room temperature for up to 24 hours. **Throw away (dispose of) any NIVESTYM prefilled syringe that has been left at room temperature for longer than 24 hours.**
- After you inject your dose, throw away (dispose of) any unused NIVESTYM left in the prefilled syringe. **Do not** save unused NIVESTYM in the prefilled syringe for later use.
- **Keep NIVESTYM and all medicines out of the reach of children.**

Using your prefilled syringe

- It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.
- You should not inject a dose of NIVESTYM less than 0.3 mL (180 mcg) from a NIVESTYM prefilled syringe. A dose less than 0.3 mL cannot be accurately measured using the NIVESTYM prefilled syringe.
- Make sure the name NIVESTYM appears on the carton and prefilled syringe label.
- **Do not use a NIVESTYM prefilled syringe after the expiration date on the label.**
- **Do not shake the NIVESTYM prefilled syringe.**
- The prefilled syringe has a needle guard that needs to be activated to cover the needle after the injection is given. The needle guard will help prevent needle stick injuries to anyone who handles the prefilled syringe.
- **Do not** remove the needle cover from the prefilled syringe until you are ready to inject.
- Do not use the NIVESTYM prefilled syringe if the needle cover is missing.
- **Do not** use the prefilled syringe if the carton is open or damaged**.**
- **Do not** use a prefilled syringe if it has been dropped on a hard surface. The prefilled syringe may be broken even if you cannot see the break. Use a new prefilled syringe.

Call your healthcare provider if you have any questions.

About the NIVESTYM prefilled syringe

- NIVESTYM prefilled syringes come in two strengths. Depending on your prescription, you will receive NIVESTYM prefilled syringes that contain 300 mcg/0.5mL or 480 mcg/0.8mL of medicine. Your healthcare provider will determine the dose in milliliters (mL) that you will need to give based on your body weight.

- When you receive your NIVESTYM prefilled syringes, always check to see that the:
  - name NIVESTYM appears on the carton and prefilled syringe label.
  - expiration date on the prefilled syringe label has not passed. **You should not use a prefilled syringe after the date on the label.**
  - strength of NIVESTYM (number of micrograms on the carton containing the prefilled syringe) is the same as what your healthcare provider prescribed.

NIVESTYM prefilled syringe parts (see Figure A).
NIVESTYM 300 mcg/0.5mL prefilled syringe is shown as an example.

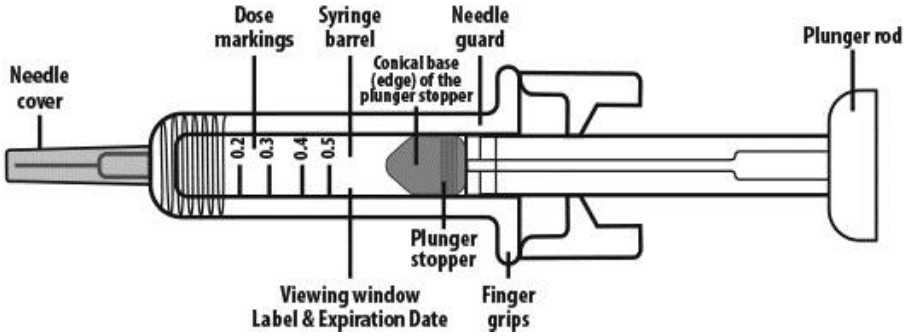

Figure A

What you need for your injection

Included in the carton:
- 1 new NIVESTYM prefilled syringe

Not included in the carton (see Figure B)
- 1 adhesive bandage
- 1 alcohol wipe
- 1 cotton ball or gauze
- sharps disposal container

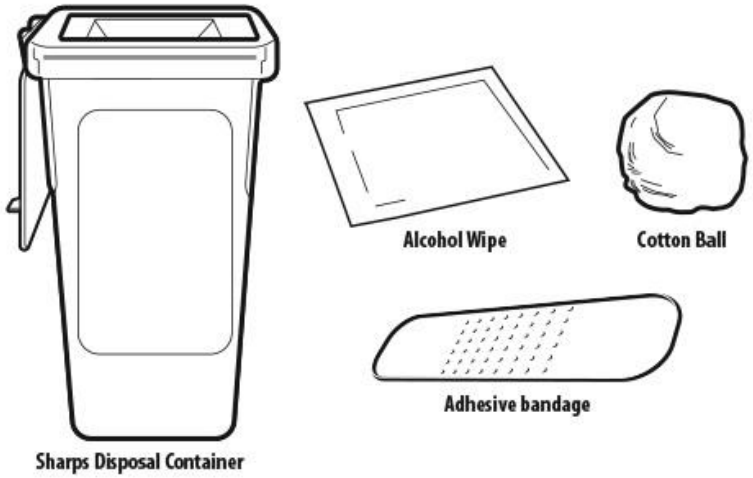

Figure B

Figure C shows a needle guard that has not yet been activated. The prefilled syringe is ready for use. This is what the prefilled syringe looks like before use.

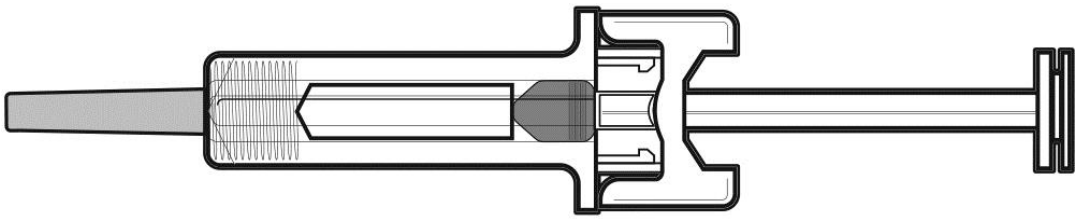

Figure C

Figure D shows a needle guard that has been activated. This is what the prefilled syringe looks like after use.

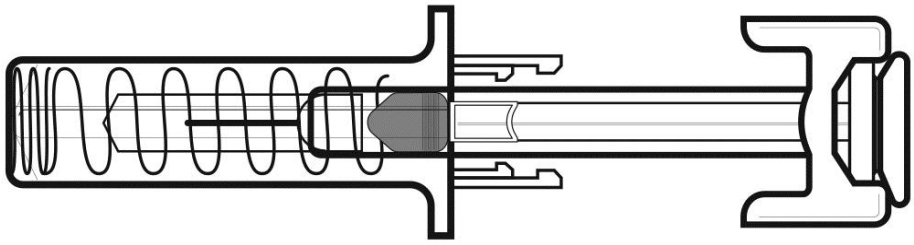

Figure D

Preparing the NIVESTYM prefilled syringe

Step 1: Find a clean, well-lit flat work surface.

Step 2: Take the carton containing the NIVESTYM prefilled syringe out of the refrigerator and leave it unopened on your work surface for at least 30 minutes so that it reaches room temperature. Put the original carton with any unused prefilled syringes back in the refrigerator.

- **Do not shake the prefilled syringe.**
- **Do not leave the prefilled syringe in direct sunlight.**

Step 3: Wash your hands with soap and water.

Step 4: Remove the prefilled syringe from the carton. Check to make sure that the needle guard is covering the barrel of the prefilled syringe. **Do not push the needle guard over the needle cover before the injection.** This may activate or lock the needle guard. See Figure C above that shows how the prefilled syringe looks before use.

If the needle guard is covering the needle that means it has been activated. See Figure D above that shows how the prefilled syringe looks after use. **Do not use the NIVESTYM prefilled syringe.** Get another prefilled syringe that has not been activated and is ready to use.

Step 5: Check the expiration date on the NIVESTYM prefilled syringe. **Do not use the NIVESTYM prefilled syringe if the expiration date has passed.**

Step 6: Inspect the medicine and prefilled syringe. Turn the prefilled syringe so you can see the medicine and markings in the window. Look through the window on the NIVESTYM prefilled syringe. Make sure the medicine in the prefilled syringe is clear and colorless.

- **Do not use the NIVESTYM prefilled syringe if:**
  - The medicine is cloudy or discolored or contains flakes or particles.
  - Any part of the prefilled syringe appears cracked or broken.
  - The prefilled syringe has been dropped.
  - The needle cover is missing or not securely attached.
  - The expiration date printed on the label has passed.
- In all cases, use a new prefilled syringe and call your healthcare provider.

Step 7: Choose the injection site

- When giving your injections, follow your healthcare provider's instructions about changing the site for each injection.
- Areas of your body that you may use as injection sites include (See Figure E):
  - front of your thigh
  - stomach area (abdomen), except for a 2-inch area around your navel (belly button)
  - outer upper outer arms, only if a caregiver is giving you the injection
  - upper outer area of your buttocks, only if a caregiver is giving you the injection

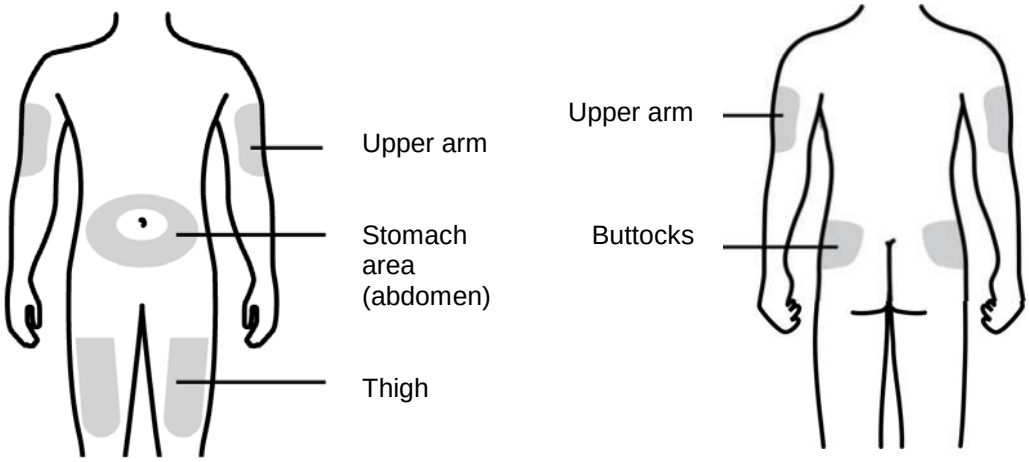

Figure E

  - Choose a different site for each injection of NIVESTYM.
  - **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

Step 8: Clean your injection site with an alcohol wipe. See Figure F.

- Let your skin dry.
- **Do not** touch this area again before injecting.

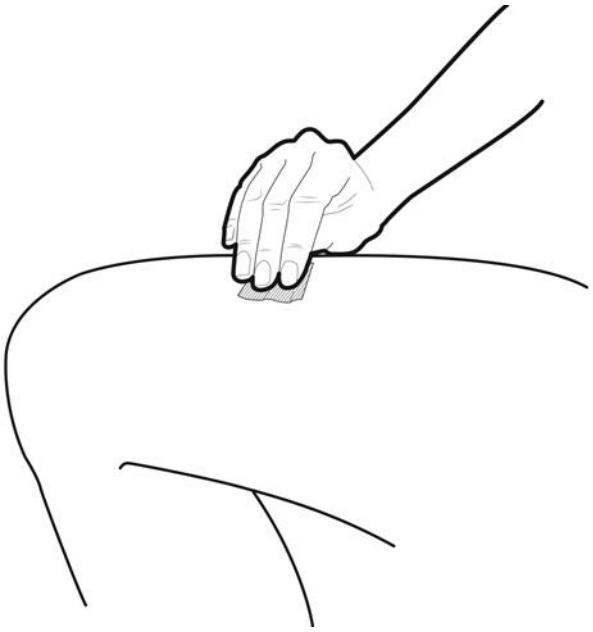

Figure F

Step 9: Hold the prefilled syringe by the needle guard with the needle cover pointing up. Carefully pull the needle cover straight off and away from your body. Throw away the needle cover. **Do not recap the needle.** See Figure G.

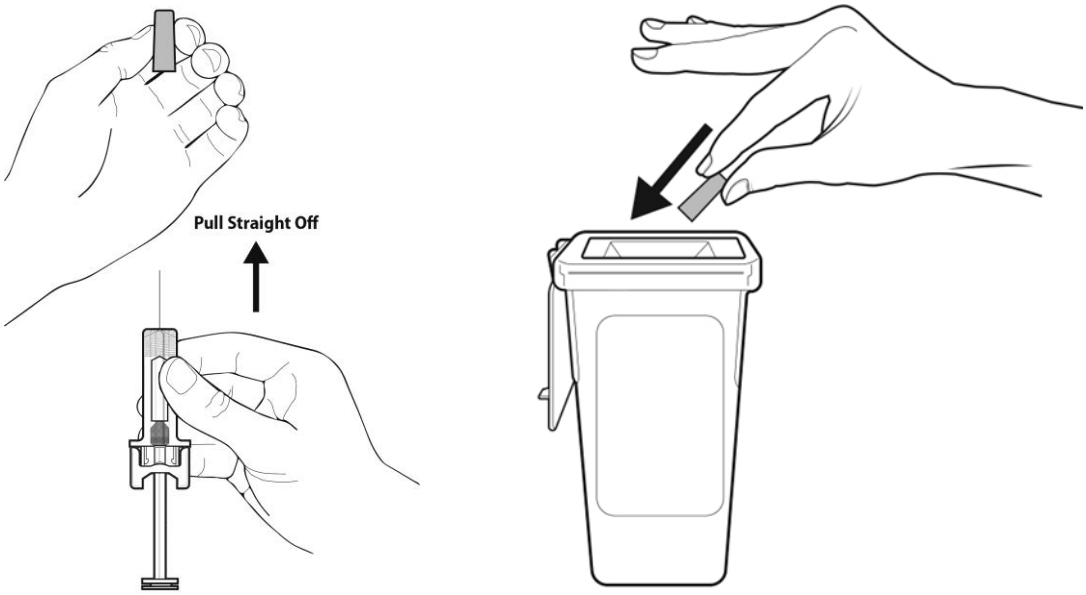

Figure G

Your healthcare provider has prescribed either a “full” syringe dose or a “partial” syringe dose.

- If you are prescribed a partial dose of NIVESTYM, follow Steps 10 through 18.
- If you are prescribed a full dose, you will inject **all** of the medicine from your prefilled syringe. For a full dose, skip Steps 10 and 11, and follow Steps 12 through 18.

Partial dosing

Step 10: Point the needle up and tap gently until the air rises to the top. See Figure H.

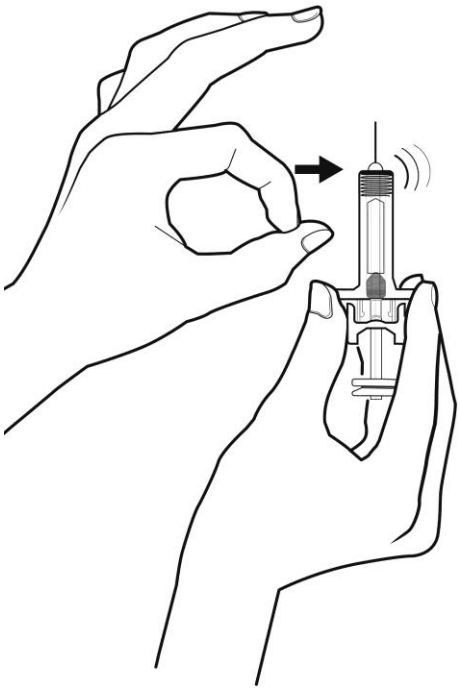

Figure H

Step 11: Holding the prefilled syringe as shown, slowly push up on the plunger rod to push out the extra air and medicine until the end of the conical base (edge) of the plunger stopper lines up with the syringe marking for your prescribed dose. See Figure I for an example of a dose of 0.3 mL. Your dose may be different than the example shown.

Be careful not to activate the needle guard before use. **Do not use a NIVESTYM prefilled syringe that has been activated.**

Check again to make sure the correct dose of NIVESTYM is in the prefilled syringe.

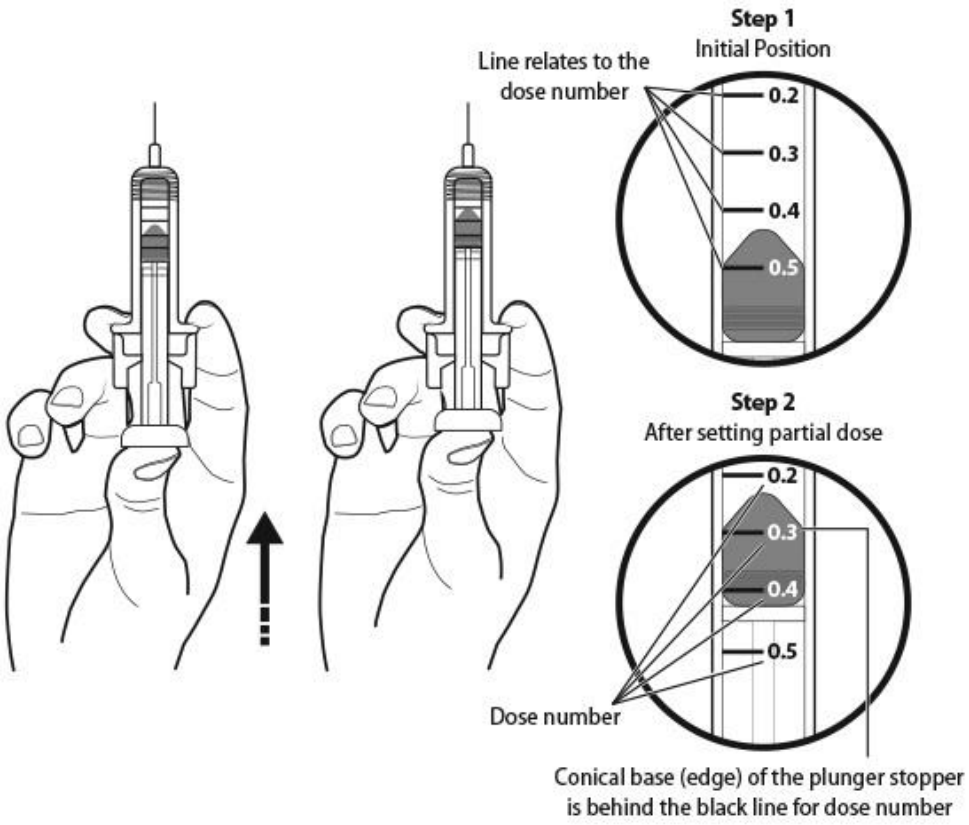

Figure I

Administering the NIVESTYM prefilled syringe

Step 12: With one hand, gently pinch a fold of skin at the injection site. Hold the pinch. See Figure J.

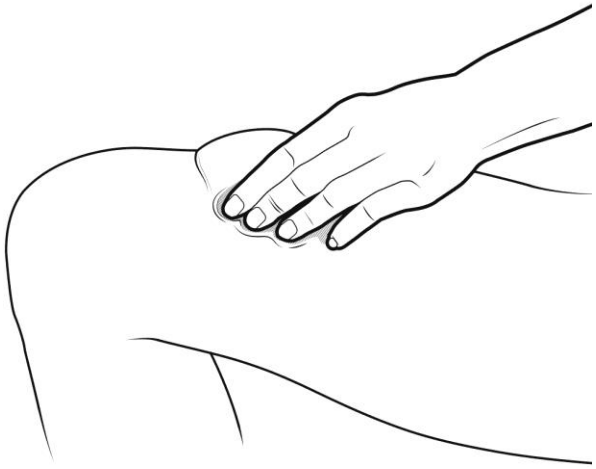

Figure J

Step 13: With your other hand, hold the prefilled syringe like you would hold a pencil. Use a quick "dart-like" motion to insert the needle at a 45 to 90 degree angle into the skin as shown. See Figure K.

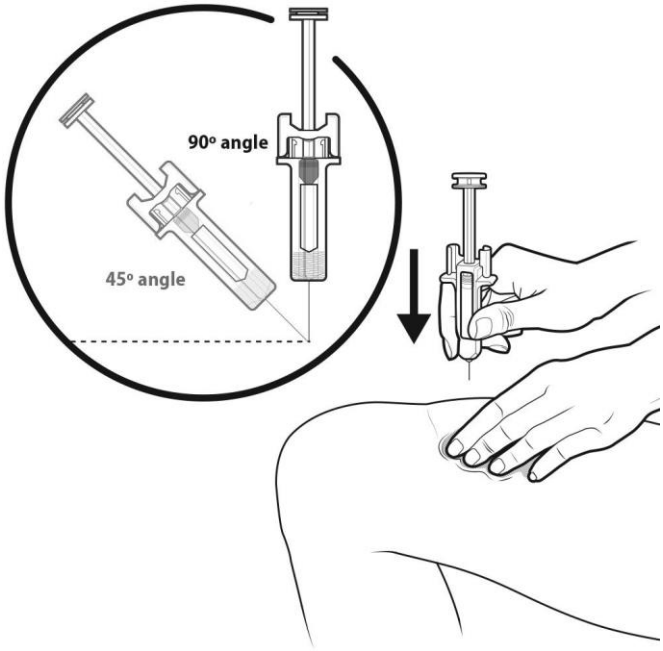

Figure K

Step 14: Using slow and constant pressure, press down on the plunger rod as far as it will go. Keep the plunger rod fully pressed down while you hold the prefilled syringe in place for 5 seconds. See Figure L.

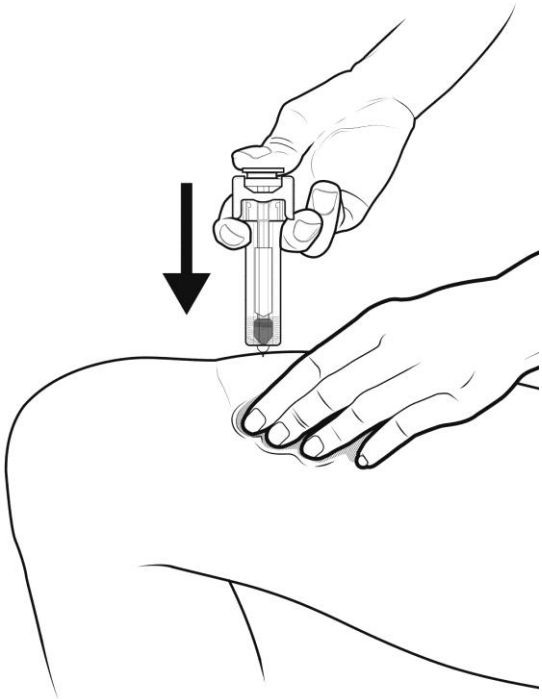

Figure L

Step 15: Keep the plunger rod fully pressed down while you carefully pull the needle straight out from the injection site. See Figure M.

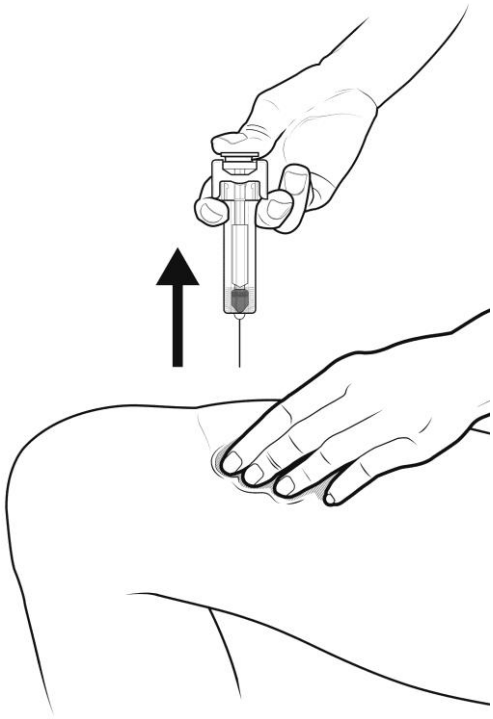

Figure M

Step 16: As you let go of the plunger rod, the needle guard will automatically slide over the needle until the needle is completely covered and the needle guard locks into place. **Do not recap the needle.** See Figure N.

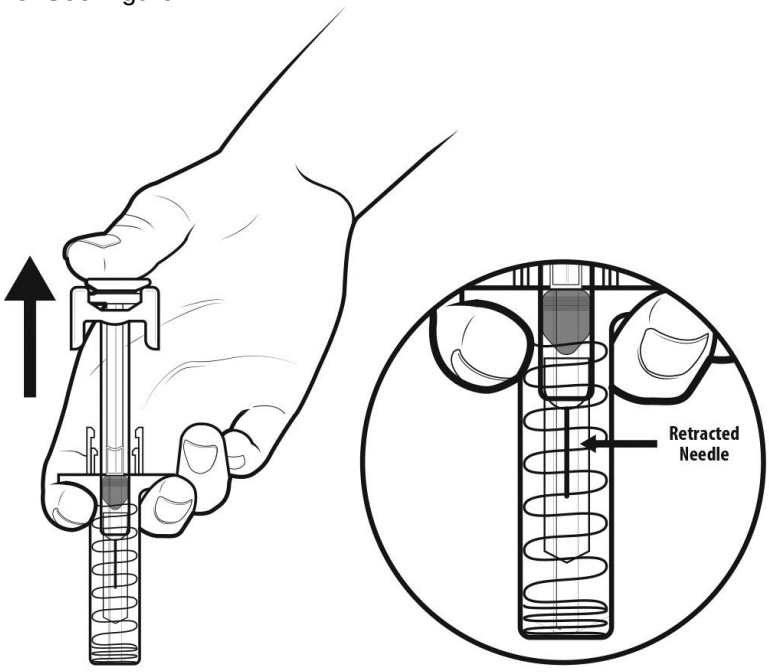

Figure N

Step 17: There may be a small amount of blood at the injection site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may cover the injection site with a small adhesive bandage, if needed. See Figure O.

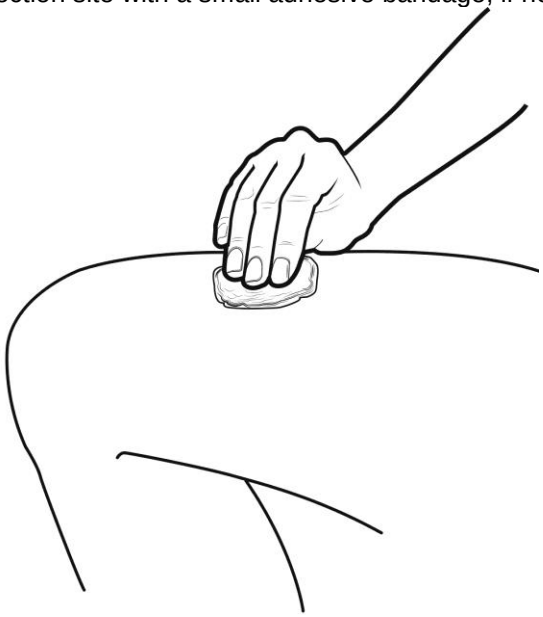

Figure O

Step 18: Throw away (dispose of) the syringe as instructed by your healthcare provider or by following the instructions below. See Figure P.

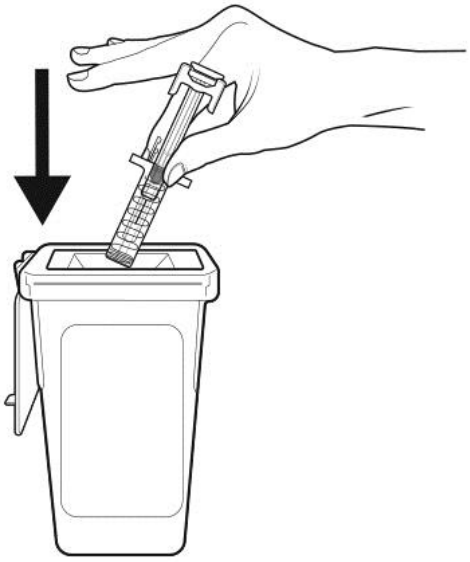

Figure P

Disposing of (throw away) used NIVESTYM prefilled syringes

- Put the used prefilled syringe in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of)** prefilled syringes in your household trash.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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LAB-0938-0.2
For more information go to www.pfizer.com or call 1-800-438-1985.

Issued: 7/2018

Instructions for Use
NIVESTYM
(Neye-ves-tim)
(filgrastim-aafi)
injection
Single-Dose Vial

Important

Read the Patient Information for important information you need to know about NIVESTYM before using these Instructions for Use.

Before you use a NIVESTYM vial, read this important information:
Storing your NIVESTYM vial

- Store the vial in the refrigerator between 36˚F to 46˚F (2˚C to 8˚C).
- **Do not** freeze.
- Keep the vial in the original carton to protect from light or physical damage.
- Take the vial out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- Throw away (dispose of) any vial that has been left at room temperature for longer than 24 hours.
- After you inject your dose, throw away (dispose of) any unused NIVESTYM left in the vial. **Do not** save unused NIVESTYM in the vial for later use.

Keep NIVESTYM and all medicines out of the reach of children.

Using your vial

- **It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.**
- Make sure the name NIVESTYM appears on the carton and vial label.
- **Only use the vial 1 time. Discard (throw away) the vial with any remaining NIVESTYM liquid.**
- **Do not** use a vial after the expiration date on the label.
- **Do not** shake the vial.
- **Do not** use the vial if the medicine is cloudy or discolored or contains flakes or particles.

Call your healthcare provider if you have any questions.

Step 1: Prepare

A Remove the vial from the refrigerator.

Find a clean, well-lit, flat work surface. Place the vial on your clean work surface for **30** minutes and allow it to reach room temperature before you give an injection.

Do not try to warm the vial by using a heat source such as hot water or microwave.

- **Do not** leave the vial in direct sunlight.
- **Do not** shake the vial.
- Use the vial only 1 time.

B Inspect the vial.

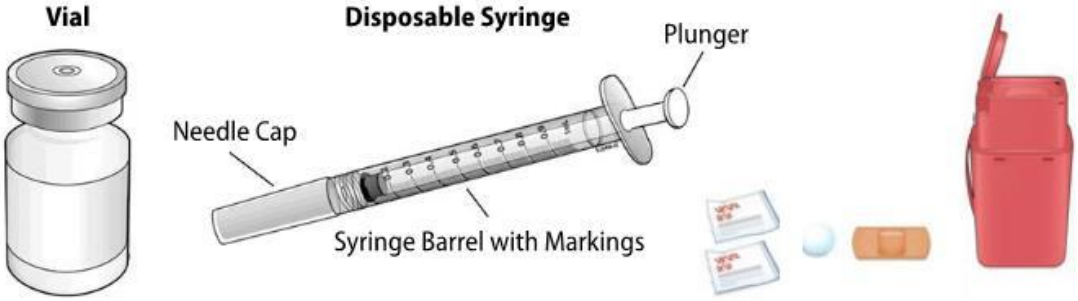
Make sure the medicine in the vial is clear and colorless.

- **Do not** use the vial if:
  - The medicine is cloudy or discolored or contains flakes or particles.
  - The expiration date printed on the label has passed.
- In all cases, use a new vial and call your healthcare provider.

C Gather all materials needed for your injection.

Wash your hands thoroughly with soap and water. On your clean, well-lit, flat work surface, place:

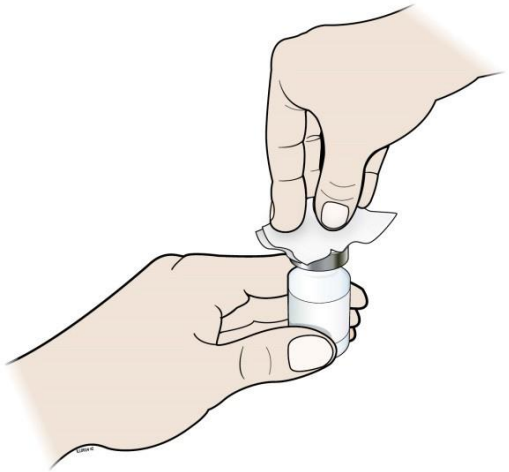
- 1 Vial
- 1 Disposable syringe and needle
- 2 Alcohol wipes
- 1 Cotton ball or gauze pad
- 1 Adhesive bandage
- Sharps disposal container



- **Only use the disposable syringes and needles that your healthcare provider prescribes.**
- **Only use the syringes and needles 1 time. Throw away (dispose of) any used syringes and needles. See Step 5 Finish, for instructions about how to properly dispose of used syringes and needles.**
- You should only use a syringe that is marked in tenths of milliliters (mL).
- Your healthcare provider will show you how to measure the correct dose of NIVESTYM. This dose will be measured in milliliters (mL).

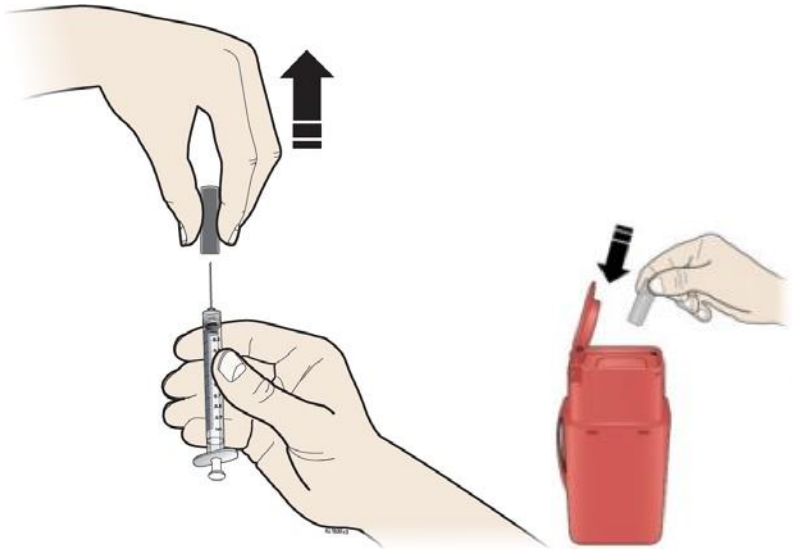
Step 2: Get Ready

D Take the cap off the vial. Clean the rubber stopper with 1 alcohol wipe.



E Check the carton containing the needle and syringe. If the carton has been opened or damaged, do not use that needle and syringe. Dispose of (throw away) that needle and syringe in the sharps disposal container.

F Hold the syringe by the barrel with the needle cap pointing up. Carefully pull the needle cap straight off and away from your body.

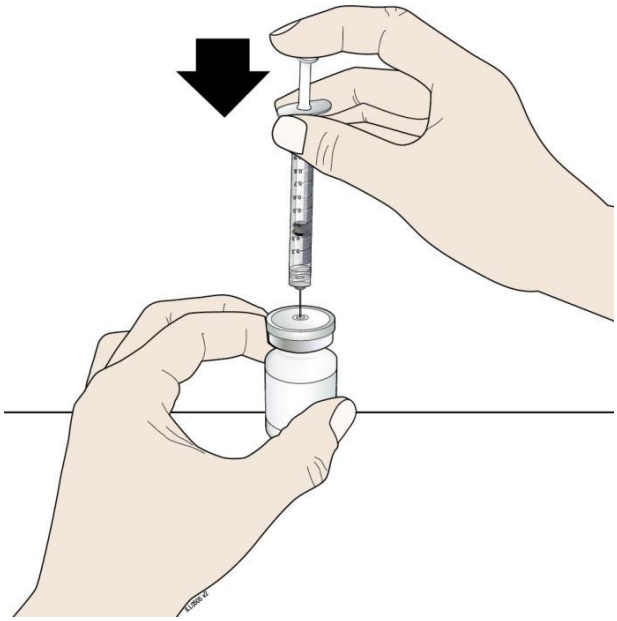


Pull back on the plunger and draw air into the syringe that is the same amount (mL) as the dose of NIVESTYM that your healthcare provider prescribed.

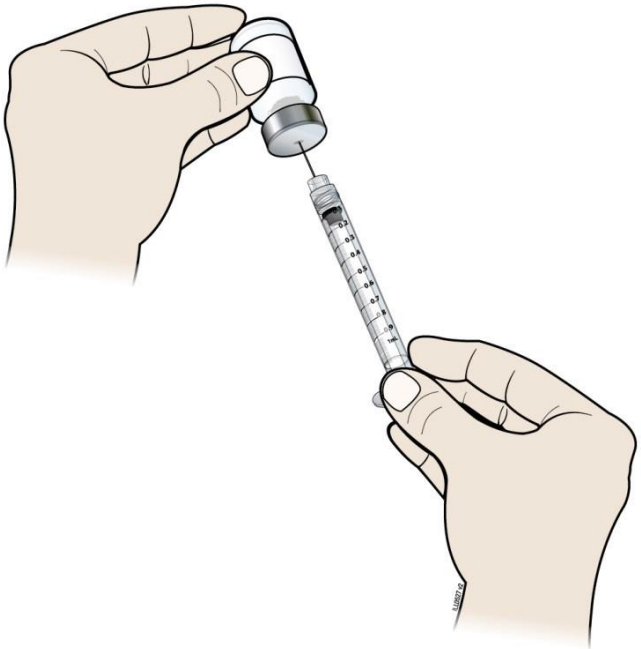
Important: Throw away the needle cap into the sharps disposal container. Do not recap the needle.

G Keep the vial on the flat work surface and insert the needle straight down through the rubber stopper. Do not insert the needle through the rubber stopper more than 1 time.

H Push the plunger down and inject all the air from the syringe into the vial of NIVESTYM.

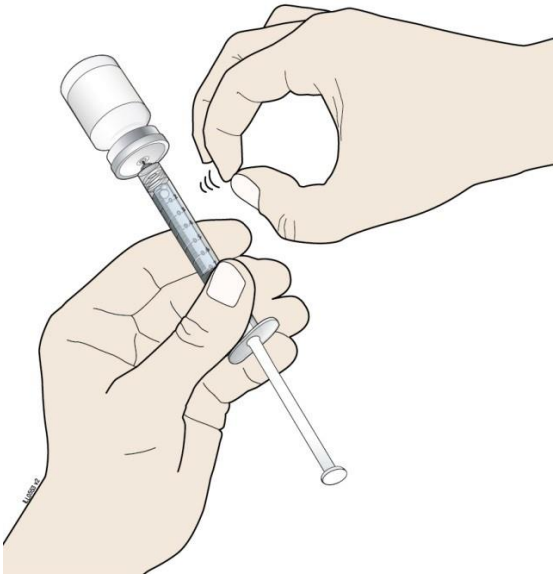


I Keep the needle in the vial and turn the vial upside down. Make sure that the NIVESTYM liquid is covering the tip of the needle.



J Keep the vial upside down and slowly pull back on the plunger to fill the syringe barrel with NIVESTYM to the correct marking amount (mL) of medicine that matches the dose your healthcare provider prescribed.

K Keep the needle in the vial and check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe barrel with your finger until the air bubbles rise to the top. Slowly push the plunger up to push the air bubbles out of the syringe.

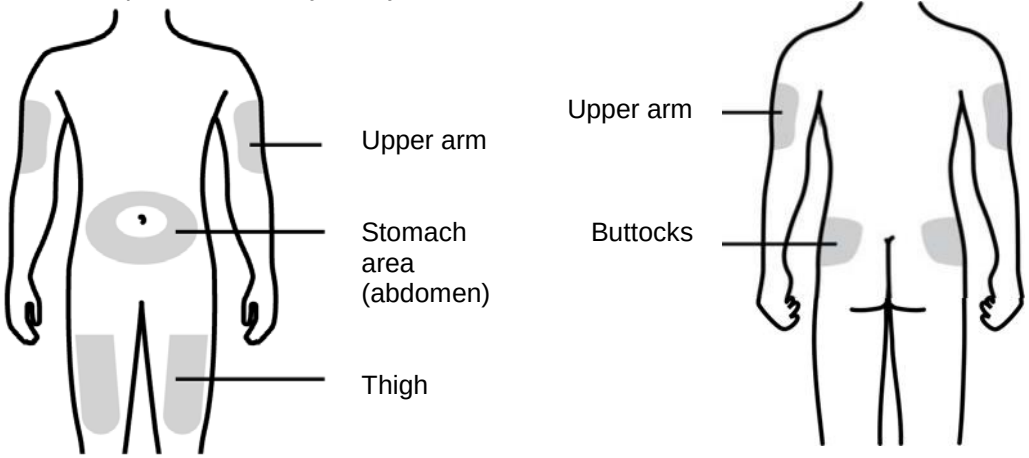


L Keep the tip of the needle in the liquid and again pull the plunger back to the number on the syringe barrel that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of NIVESTYM. If there are still air bubbles, repeat the steps above to remove them.

M Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your healthcare provider. Do not remove the needle from the vial. Lay the vial down on its side with the needle still in the vial.

Step 3: Select and Prepare the Injection Site

N Prepare and clean your injection site.



You can use:

- Thigh
- Stomach area (abdomen), except for a **2**-inch area right around your navel (belly button)
- Upper outer area of your buttocks (only if someone else is giving you the injection)
- Outer area of upper arm (only if someone else is giving you the injection)

Clean your injection site with a clean alcohol wipe.

- Let your skin dry.
- **Do not** touch this area again before injecting.
- If you want to use the same injection site, make sure it is not the same spot on the

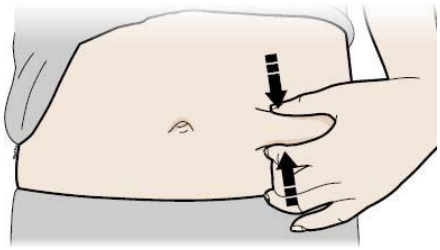
injection site area you used for a previous injection.

- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

Step 4: Subcutaneous (under the skin) injection

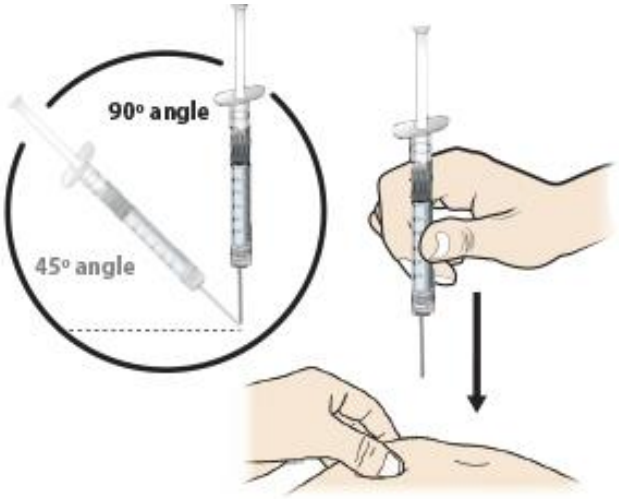
O Remove the prepared syringe and needle from the vial.

P Pinch your injection site to create a firm surface.

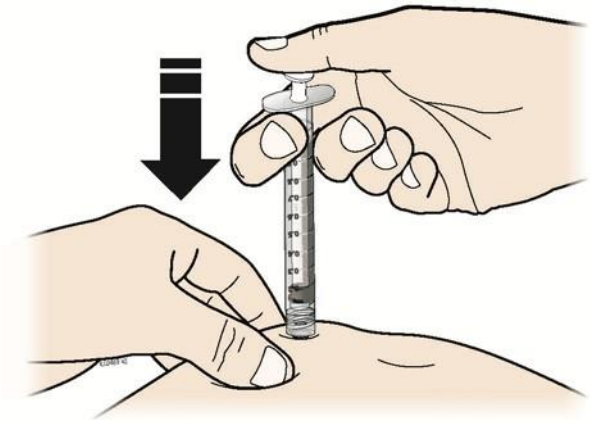


Important: Keep skin pinched while injecting.

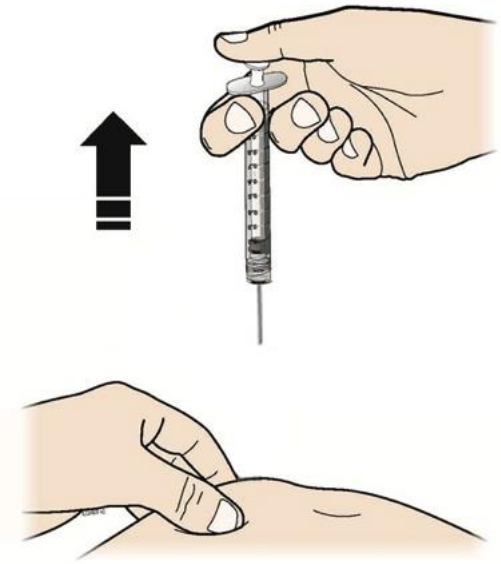
Q Hold the pinch. Insert the needle into the skin at a 45 to 90 degree angle.



R Using slow and constant pressure, push the plunger until it reaches the bottom.



When done gently pull the needle out of the injection site at the same 45 to 90 degree angle used to insert it.



Step 5: Finish

S Dispose of (throw away) the used needle and syringe.

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose** needles, and syringes in your household trash.

- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal

in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

T Examine the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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